MedicalXpress

Native American ancestry linked to greater risk of relapse in young leukemia patients

February 6 2011

The first genome-wide study to demonstrate an inherited genetic basis for racial and ethnic disparities in cancer survival linked Native American ancestry with an increased risk of relapse in young leukemia patients. The work was done by investigators at St. Jude Children's Research Hospital and the Children's Oncology Group (COG).

Along with identifying Native American ancestry as a potential new marker of poor treatment outcome, researchers reported evidence the added risk could be eliminated by administering an extra phase of chemotherapy. The study involved 2,534 children and adolescents battling acute lymphoblastic leukemia (ALL), the most common childhood cancer. The work appears in the February 6 advance online edition of the scientific journal *Nature Genetics*.

The children were all treated in protocols conducted by St. Jude or COG. Although the overall cure rate for childhood ALL now tops 80 percent, and is close to 90 percent at St. Jude, racial and ethnic disparities have persisted. Based on self-declared status, African-American and Hispanic children with the disease have often fared worse than their white and Asian counterparts. This is the first study to use genomics to define ancestry, rather than relying on self-declared racial or ethnic categories.

"To overcome racial disparity you have to understand the reasons behind it," said Jun Yang, Ph.D., St. Jude Department of Pharmaceutical Sciences assistant member and the study's first author. "While genetic ancestry may not completely explain the racial differences in relapse risk

or response to treatment, this study clearly shows for the first time that it is a very important contributing factor."

This study identified a possible mechanism linking ancestry and relapse. Hispanic patients, who have a high percentage of Native American ancestry, were more likely than other patients to carry a version of the PDE4B gene that was also strongly associated with relapse. The PDE4B variants were also linked with reduced sensitivity to glucocorticoids, medications that play a key role in ALL treatment. "This is just one example of how ancestry could affect relapse risk," said the study's senior author Mary Relling, Pharm.D., St. Jude Pharmaceutical Sciences chair. "It is likely that many other genes are involved."

Investigators also found ALL patients with greater Native American ancestry who received additional chemotherapy as part of a COG clinical trial benefited more from the extra treatment than other children. "These are important steps on the way to personalized cancer care, whereby treatment can be tailored to provide maximal benefit to patient subgroups, and someday, individual patients," said co-author Stephen Hunger, M.D., University of Colorado professor of pediatrics and chair of COG's ALL committee.

For this study, scientists used a library of 444,044 common genetic variations known as single nucleotide polymorphisms, or SNPs, to search each patient's DNA for evidence linking ancestry and relapse. The study found that cancer was 59 percent more likely to return in patients whose genetic makeup reflected at least 10 percent Native American ancestry.

About 25 percent of patients in this study met the 10 percent threshold. The percentage was highest among the self-reported Hispanic and Native American patients, who have been reported to be at higher risk of relapse.

Native American ancestry identified patients at high risk of relapse missed by current clinical tools, including testing for minimal residual disease (MRD), which measures the cancer cells that survive the initial round of therapy. Relling said additional research is needed to confirm the findings before screening becomes part of clinical care.

This study used advances in high throughput genomic technologies to better understand why cancer treatment sometimes fails and how the failure is related to genetic ancestry. Unlike previous research that relied on patient self-reports of race and ethnicity and focused on specific populations, this study focused on a group of patients as diverse as the U.S. and representative of the nation's entire ALL population.

Provided by St. Jude Children's Research Hospital