

Ancient DNA Reveals Origin of Racial/Ethnic Disparity in a Childhood Cancer

Researchers discovered a genetic variant linked with higher rates of acute lymphoblastic leukemia (ALL) in Latino children.

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There are 40% more Hispanic/Latino kids diagnosed with acute lymphoblastic leukemia (ALL) than white non-Hispanic/Latino children; actually, Hispanic/Latino individuals have the highest risk of ALL in the United States. However, the basis for this difference is not well understood. Researchers recently identified a genetic variant that accounts for the increased risk of B-cell ALL in Hispanic/Latino children, and using ancient DNA, they traced the mutation all the way back to the first migrants who entered the Americas [about] 13,000 years ago.

“We were able to use genetic studies in diverse populations to identify this new risk factor that explains some of the population differences in ALL risk,” says [Vijay Sankaran, MD, PhD](#), a lead author of the study and a physician-scientist at the [Dana-Farber/Boston Children’s Cancer and Blood Disorders Center](#). The findings were published in [Cell Genomics](#) on March 26 and are a close collaboration with colleagues at the University of Southern California.

Sankaran and colleagues employed genome-wide association studies (GWAS) to look for mutations contributing to racial/ethnic differences in B-cell ALL. The team discovered a genetic variant that explains a significant portion of the increased risk in Hispanic/Latino kids. The mutation reduces the expression of a gene called IKZF1, which encodes for the protein Ikaros that is required for B-cell development. The mutation is found at a much lower frequency in white non-Hispanic/Latino children.

Sankaran, an Associate Member at the Broad Institute, and his laboratory, led by postdoctoral fellow [Lara Wahlster, MD PhD](#), provide functional data that suggest the variant slows B-cell maturation and, in turn, increases the chances of a cancerous mutation popping up in the cells.

Hispanic/Latino individuals in the United States are known to have diverse ancestral origins, and the researchers found that this risk variant appeared to arise from Indigenous American ancestral origins. On the other hand, the variant was nearly absent in people with European ancestry. This observation may explain the higher prevalence of ALL in some countries in Latin America, such as

Mexico, where there is a greater contribution of Indigenous American ancestry, compared to countries like Argentina, where there is a lower contribution of such ancestry.

The researchers then analyzed ancient DNA samples to understand when the risk variant arose in human history. The oldest previously sequenced ancient DNA from an Indigenous American individual, found at the Anzick site in Montana, carried the mutation. This means the risk variant was present among the first migrants who entered the Americas approximately 13,000 years ago.

Further investigation revealed that the variant was promoted by natural selection. Sankaran and colleagues speculated that carrying the mutation may have protected people against infection since IKZF1 plays a role in immune function.

“Exploring ancient DNA provides insights into the roots of modern-day health differences, bridging the gap between our past and the pressing health challenges facing our society today,” says Sankaran.

The study’s findings may provide insights into the higher rates of treatment resistance and relapse observed in Hispanic/Latino children with ALL. Sankaran emphasizes the need for further research to gain a comprehensive understanding of the implications of this variant. Ultimately, Sankaran hopes this knowledge may lead to ways of preventing leukemia from developing in a child carrying the identified genetic variant.

“I hope our work will ultimately pave the path towards preventing this disease,” says Sankaran.

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