

IKZF1 gene mutations found to increase hereditary risk for ALL in children

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A late-breaking abstract being presented today during the 58th American Society of Hematology (ASH) Annual Meeting and Exposition in San Diego identifies inherited genetic mutations in the gene *IKZF1* that confer a higher likelihood of developing pediatric acute lymphocytic leukemia (ALL). The findings are among the latest evidence to point to a strong inherited genetic basis of ALL risk in children. Some of the variants identified also appear to reduce cancer cells' sensitivity to a chemotherapy drug used to treat some types of ALL, potentially contributing to drug resistance.

"The genetic variants help explain why these children develop leukemia and also inform potential risk for ALL in [family members](#) who carry the same defective version of *IKZF1*," said lead study author Michelle L. Churchman, PhD, of St. Jude Children's Research Hospital in Memphis. "If patients are identified as having one of these deleterious *IKZF1* mutations, then that could potentially inform their treatment, whether family members need to get screened, or other clinical decisions."

Overall, about 85 percent of children survive for at least five years after being diagnosed with ALL, a cancer affecting the lymphocytes, a type of white blood cell. Only a handful of other genes have been identified that appear to be associated with a predisposition to the disease. The new study was initiated after multiple cases of pediatric ALL were reported in a single family in Germany and a genetic analysis of the family members pointed to an inherited mutation in *IKZF1* as a possible contributor. The *IKZF1* gene encodes Ikaros, a protein with essential

roles in lymphocyte development. Previous studies have found defects in *IKZF1* in leukemia cells linked with some high-risk forms of ALL that respond poorly to treatment, such as BCR-ABL1 (Philadelphia chromosome) ALL.

The researchers sequenced the *IKZF1* gene in germline DNA from normal blood samples of more than 5,000 children with ALL treated by St. Jude Children's Research Hospital and other collaborating institutions in the Children's Oncology Group and identified 28 gene variants. They then introduced these variant forms of *IKZF1* into cultured cells to gauge their effects on activity of the Ikaros protein, cell growth and behavior, and response to chemotherapeutic agents. The results showed that most of the gene variants caused abnormalities conducive to the development of leukemia, such as increased cellular aggregation and "stickiness" of cells in the bone marrow. Several variants significantly reduced the sensitivity of leukemic cells to the chemotherapy drug dasatinib, a drug commonly used to treat high-risk forms of ALL such as BCR-ABL1.

"Leukemia running in families may be more common than was previously appreciated," said Dr. Churchman. "This is now a very active area of research, and I think we're looking at the tip of the iceberg in terms of genetic predisposition to this type of leukemia, and maybe other types as well. We now have a handful of genes identified, and I think that there will be more to come."

The team plans to continue to study the clinical outcomes of patients with *IKZF1* variants, further assess the degree to which these mutations increase the risk of ALL in families, and integrate different types of genomic studies for a more complete picture of how these mutations are inherited.

More information: Michelle L. Churchman, PhD, St. Jude Children's Research Hospital, Memphis, Tenn. will present this study, titled

"Germline Genetic Variation in IKZF1 and Predisposition to Childhood Acute Lymphoblastic Leukemia," as a late-breaking abstract (LBA-2) on Tuesday, December 6 in Hall AB of the San Diego Convention Center.

Provided by American Society of Hematology

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