

Family ties: Inherited genetic variants increase risk of Hodgkin lymphoma

September 8 2022



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"Why did my child get cancer?"

Clinicians have longed for a way to help answer this question. Doctors knew Hodgkin lymphoma sometimes occurs in families, but why this happens has been a mystery. Scientists at St. Jude Children's Research

Hospital have now helped solve it. The researchers studied multiple families affected by Hodgkin lymphoma and identified genetic variants linked to an increased risk of developing the disease. The findings appeared as a first edition in *Blood*.

Hodgkin lymphoma is a [cancer](#) of the lymphatic system (part of the immune system) that affects lymph nodes but can spread to the spleen, liver, bone marrow and lungs. As many as 7,000 new cases of the disease are diagnosed in the United States each year. Hodgkin lymphoma is the most common type of cancer in adolescents and has a five-year survival rate of 90-95%.

"We've never been able to tell these families anything other than it's just bad luck because nobody knew why more than one family member would develop Hodgkin lymphoma," said co-first and co-corresponding author Jamie Flerlage, M.D., St. Jude Department of Oncology. "We took on this study because understanding what is causing cancer in these families will help us to better counsel people about their chances of passing on genetic risk to their offspring, as well as help us identify novel targets that might potentially be used to create new treatments."

Family pedigrees help reveal variants

To study Hodgkin lymphoma occurrences in families, the researchers created pedigrees, a type of diagram that reveals familial connections while tracking the incidences of cancer. The selection criteria required two or more first-degree relatives with Hodgkin lymphoma, one of whom needed to be younger than 21 years of age when diagnosed.

Scientists performed [whole genome sequencing](#) on 234 members of 36 families and identified 44 variants (33 coding and 11 noncoding) that increase the risk of developing Hodgkin lymphoma. The findings included novel gene variants that had not been previously linked to

predisposition to the disease, such as PAX5, GATA3, IRF7, EEF2KMT and POLR1E as well as known variants such as KDR and KLHDC8B.

"Inherited variants can be an important missing piece of the puzzle when you're trying to understand why certain people are more likely to get a type of cancer," said co-corresponding author Jun J. Yang, Ph.D., St. Jude Comprehensive Cancer Center Hematologic Malignancies Program. "Whole genome sequencing that allows you to look beyond the main genetic variants to the non-coding or epigenetic variants is a powerful tool to help explain what puts a person at a higher risk of developing Hodgkin lymphoma."

Bioinformatics behind the findings

A powerful bioinformatics pipeline created at St. Jude was essential to analyzing and tracking the variants through the family pedigrees. The process included running algorithms to identify the variants in every individual, and then taking the pedigree and tracing the variants back through the [family tree](#) to figure out which ones were related to the cancer. More than 40 annotation databases and pieces of software powered the effort, which resulted in a fast, robust pipeline to analyze familial data.

"We married several existing tools as well as customized approaches to make a pipeline that could process data from these families in a meaningful way," said co-first author Jason Myers, St. Jude Center for Applied Bioinformatics. "The work that went into making this pipeline is not specific to Hodgkin lymphoma; the pipeline can be used for any other disease where families are involved, including other types of cancer and neurological disorders such as epilepsy."

The cohort of families included patients who were treated at St. Jude as well as many families who were part of a familial lifetime cohort study

pioneered by the National Cancer Institute. The analysis revealed inherited variants likely to predispose individuals to the disease in most of the families, highlighting the important role of [genetic predisposition](#) in understanding Hodgkin lymphoma.

"The family pedigrees and whole genome sequencing approach set this study apart because they allowed us to throw everything in our genomics toolkit at this question to tease apart what was happening in each family," said co-corresponding author Evadnie Rampersaud, Ph.D., St. Jude Center for Applied Bioinformatics. "We had the amazing opportunity to develop a highly comprehensive bioinformatic pipeline for interrogating coding, noncoding and copy-number variants in families. This project was a large-scale collaboration that shines brightly on the interconnective opportunities and talents within St. Jude."

More information: Jamie E Flerlage et al, Discovery of novel predisposing coding and noncoding variants in familial Hodgkin lymphoma, *Blood* (2022). [DOI: 10.1182/blood.2022016056](https://doi.org/10.1182/blood.2022016056)

Provided by St. Jude Children's Research Hospital

Citation: Family ties: Inherited genetic variants increase risk of Hodgkin lymphoma (2022, September 8) retrieved 12 June 2024 from <https://medicalxpress.com/news/2022-09-family-ties-inherited-genetic-variants.html>

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