

Inherited mutation can predispose children to a type of brain tumor

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Collaboration co-led by researchers at St. Jude Children's Research Hospital discovers a novel predisposition gene in pediatric medulloblastoma. Left to right: Paul Northcott, Giles Robinson, Kim Nichols, Brian Gudenias, Kyle Smith, all of St. Jude. Credit: St. Jude Children's Research Hospital

Investigators at St. Jude Children's Research Hospital, the European

Molecular Biology Laboratory, and the German Cancer Research Center have identified ELP1 as a novel predisposition gene in the SHH subgroup of pediatric medulloblastoma. The work appears as an advance online publication today in *Nature*.

Medulloblastoma is the most common malignant pediatric brain tumor. The SHH subgroup accounts for about 30% of all pediatric medulloblastoma cases. Previous research suggested that this subgroup is affected by [genetic predisposition](#) from abnormalities in the germline (inherited) DNA of patients. However, this prior work was restricted to known cancer [predisposition genes](#).

"The [scientific evidence](#) and the experiences of patients and families suggested to us that inherited [mutations](#) might play a bigger role than previously thought," said co-senior author Paul Northcott, Ph.D., of the St. Jude Department of Developmental Neurobiology. "By searching for genes beyond the usual suspects, we showed that a significant portion of SHH medulloblastoma with inherited mutations wasn't being recognized."

The team looked at all protein-coding genes (the exome) in more than 1,000 patients with medulloblastoma. The researchers compared their medulloblastoma findings to more than 118,000 exomes from several databases of individuals without cancer. Results showed that the gene ELP1 is abnormally mutated in the germline DNA of 14-15% of children with SHH medulloblastoma.

With the addition of ELP1 to the list of known cancer predisposition genes, the researchers showed that at least 40% of pediatric SHH medulloblastoma is driven by an inherited abnormality. ELP1 mutations occur at more than double the rate of any other previously acknowledged [cancer](#) predisposition gene in SHH medulloblastoma.

A better understanding of predisposition

ELP1 normally functions as part of a multi-subunit complex called elongator. Elongator plays a role in regulating translation, the process of translating genetic information into proteins. This finding supports investigations into how dysregulation of translation contributes to medulloblastoma.

"When multiple members of a family have the same kind of medulloblastoma, but don't have mutations in any of the recognizable predisposition genes, there has to be more to the story," said co-first author Giles Robinson, M.D., of the St. Jude Department of Oncology. "ELP1 has not been part of routine genetic testing offered to patients and families, but this work suggests that it should be included for medulloblastoma."

The researchers also found that ELP1 may help guide prognosis. Patients with this mutation tend to do well on currently available therapies. Researchers are continuing to study ELP1 in the laboratory to determine if the identified mutations could be used to tailor [medulloblastoma](#) therapy in the future.

More information: Germline Elongator mutations in Sonic Hedgehog medulloblastoma, *Nature* (2020). DOI: [10.1038/s41586-020-2164-5](https://doi.org/10.1038/s41586-020-2164-5) , [nature.com/articles/s41586-020-2164-5](https://www.nature.com/articles/s41586-020-2164-5)

Provided by St. Jude Children's Research Hospital

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