

Tumors evolve rapidly in a childhood cancer, leaving fewer obvious tumor targets

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An extensive genomic study of the childhood cancer neuroblastoma reinforces the challenges in treating the most aggressive forms of this disease. Contrary to expectations, the scientists found relatively few recurrent gene mutations—mutations that would suggest new targets for neuroblastoma treatment. Instead, say the researchers, they have now refocused on how neuroblastoma tumors evolve in response to medicine and other factors.

"This research underscores the fact that tumor cells often change rapidly over time, so more effective treatments for this [aggressive cancer](#) will need to account for the dynamic nature of neuroblastoma," said study leader John M. Maris, M.D., director of the Center for Childhood Cancer Research at The Children's Hospital of Philadelphia (CHOP).

Striking the [peripheral nervous system](#), neuroblastoma usually appears as a solid tumor in a young child's chest or abdomen. It comprises 7 percent of all childhood cancers, but causes 10 to 15 percent of all childhood cancer-related deaths. Neuroblastoma is notoriously complex, with a broad number of gene changes that can give rise to the disease.

Maris headed the multicenter research collaborative, the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative, which released its findings today in [Nature Genetics](#). This largest-ever study [genomic study](#) of a [childhood cancer](#) analyzed DNA from 240 children with high-risk neuroblastomas. Using a combination of whole-exome, whole-genome and [transcriptome](#) sequencing, the study

compared DNA from tumors with DNA in normal cells from the same patients.

Researchers at CHOP and other centers previously discovered neuroblastoma-causing mutations, such as those in the ALK gene. In the subset of patients carrying this mutation, oncologists can provide effective treatments tailored to their [genetic profile](#).

"A few years ago, we thought we would be able to sequence the genomes of individual patients with neuroblastoma, detect their specific cancer-causing mutations, and then select from a menu of treatments," said Maris. The oncology researchers designed the TARGET study to perform genomic analyses of a large cohort of high-risk neuroblastoma patients, with the goal of mapping out a limited number of treatment strategies. This approach would represent a significant step forward in personalizing neuroblastoma therapy.

However, while the researchers confirmed that roughly 10 percent of the study's neuroblastoma patients had ALK mutations, and found that a handful of other gene mutations each accounted for percentages in the single digits, there were relatively few recurrent mutations in somatic (non-germline) cells. "The relative paucity of recurrent mutations challenges the concept that druggable targets can be defined in each patient by DNA sequencing alone," wrote the authors.

In the absence of frequently altered oncogenes that drive high-risk neuroblastomas, the authors concluded that most such cases may result from other changes: rare germline mutations, copy number variations and epigenetic modifications during tumor evolution.

"Personalized medicine is more complex than we had hoped," said Maris. "While there are successes such as those in treating patients whose tumors harbor ALK mutations, this study implies that we must

think very differently about how we'll use genomics to define treatment." Maris added that neuroblastoma researchers may need to turn to functional genomics, learning which tumors will or won't respond to treatments, as well as going beyond a static picture of a cancer cell with fixed genetic contents, to devising interventions to deal with dynamic [tumor cells](#) that evolve during nervous system development.

More information: "The genetic landscape of high-risk neuroblastoma," *Nature Genetics*, Advance online publication, Jan. 20, 2013.

Provided by Children's Hospital of Philadelphia

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