Researchers find NTRK fusions more common than expected in pediatric tumors

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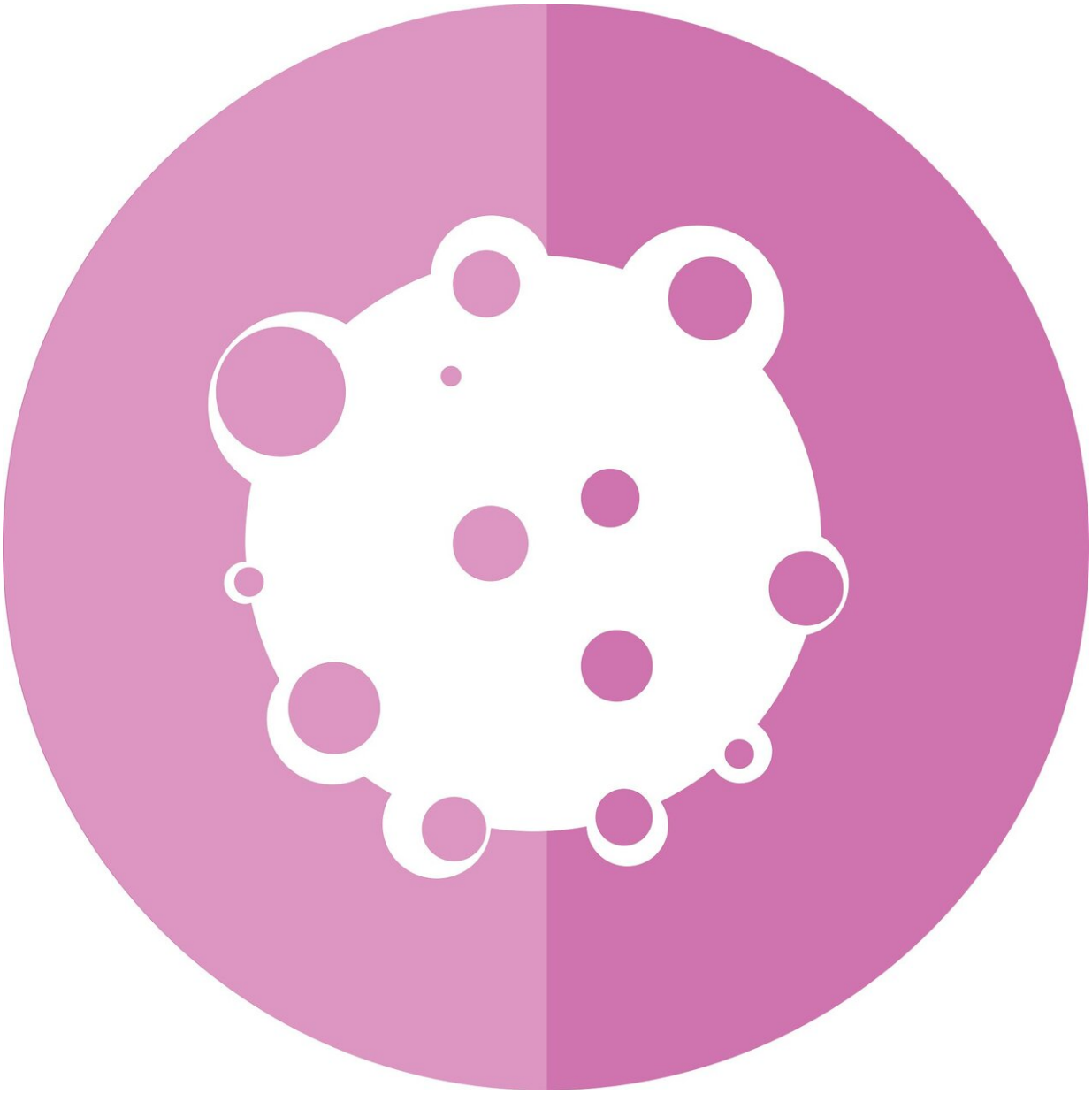

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In a large study of pediatric cancer patients, researchers from Children's Hospital of Philadelphia (CHOP) have analyzed the frequency, fusion partners, and clinical outcome of neurotrophic tyrosine receptor kinase (NTRK) fusions, which are clinical biomarkers that identify patients suitable for treatment with FDA-approved TRK inhibitors. The researchers found that NTRK fusions are more common in pediatric tumors and also involve a wider range of tumors than adult cancers, information that could help prioritize screening for NTRK fusions in pediatric cancer patients who might benefit from treatment with TRK inhibitors.

The findings were published in *JCO Precision Oncology*.

"Our findings demonstrate that NTRK fusions are far more frequently seen in pediatric tumors than in adult tumors and involve a broader panel of fusion partners and wider range of pediatric tumors than previously recognized," said senior author Marilyn M. Li, MD, Vice Chief of the Division of Genomic Diagnostics and Director of Cancer Genomic Diagnostics at CHOP. "With the recent FDA approval of larotrectinib and entrectinib for the treatment of adult and pediatric NTRK-positive, unresectable solid tumors, identification of these fusions directly impacts patient care."

Previous studies have shown that rearrangements of NTRK genes drive tumor growth in a diverse range of cancers. This led to the development of the first generation oral NTRK inhibitors, larotrectinib and entrectinib, and have spurred the development of other NTRK inhibitors, which are currently in clinical development. Ongoing clinical trials hope to identify optimal use of these drugs in children.

Given that in children, certain cancers like infantile fibrosarcoma (IF) and secretory carcinoma have very high incidence of NTRK fusions (>90%), whereas other cancers like melanoma and acute leukemia rarely involve NTRK fusions, the researchers sought to better understand the frequency of these gene fusions across all pediatric cancers.

To do so, they analyzed 1,347 consecutive pediatric tumors from 1,217 patients who underwent tumor genomic profiling using custom-designed DNA and RNA next generation sequencing panels. The researchers identified NTRK fusions in 29 tumors from 27 patients, with a positive yield of 2.22% for all tumors and 3.08% for solid tumors. NTRK fusions were detected in 13% of papillary thyroid carcinomas (PTCs), 1.9% of central nervous system (CNS) tumors, 1.8% of non-CNS, non-PTC solid tumors, and 0.4% of hematologic malignancies.

Patients in the study were followed for up to 46 months, and in almost all cases, the detection of an NTRK fusion confirmed the diagnosis of the lesion type, including five cases where the final tumor diagnosis was largely based on the discovery of an NTRK fusion. In one patient, the diagnosis was changed due to the identification of an NTRK fusion. In a separate case, a 6-month-old infant with a mass in his upper left extremity due to IF, which would have required extremely complex surgery to remove, was treated with larotrectinib and achieved complete pathologic remission.

"The identification of these NTRK fusions has facilitated precision cancer diagnosis and TRK inhibitor targeted therapy," Li said. "Our experience highlights the clinical utility of screening NTRK fusions for all pediatric tumors."

More information: Xiaonan Zhao et al, NTRK Fusions Identified in Pediatric Tumors: The Frequency, Fusion Partners, and Clinical Outcome, *JCO Precision Oncology* (2021). DOI: 10.1200/PO.20.00250

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