Change in a single DNA base drives a childhood cancer

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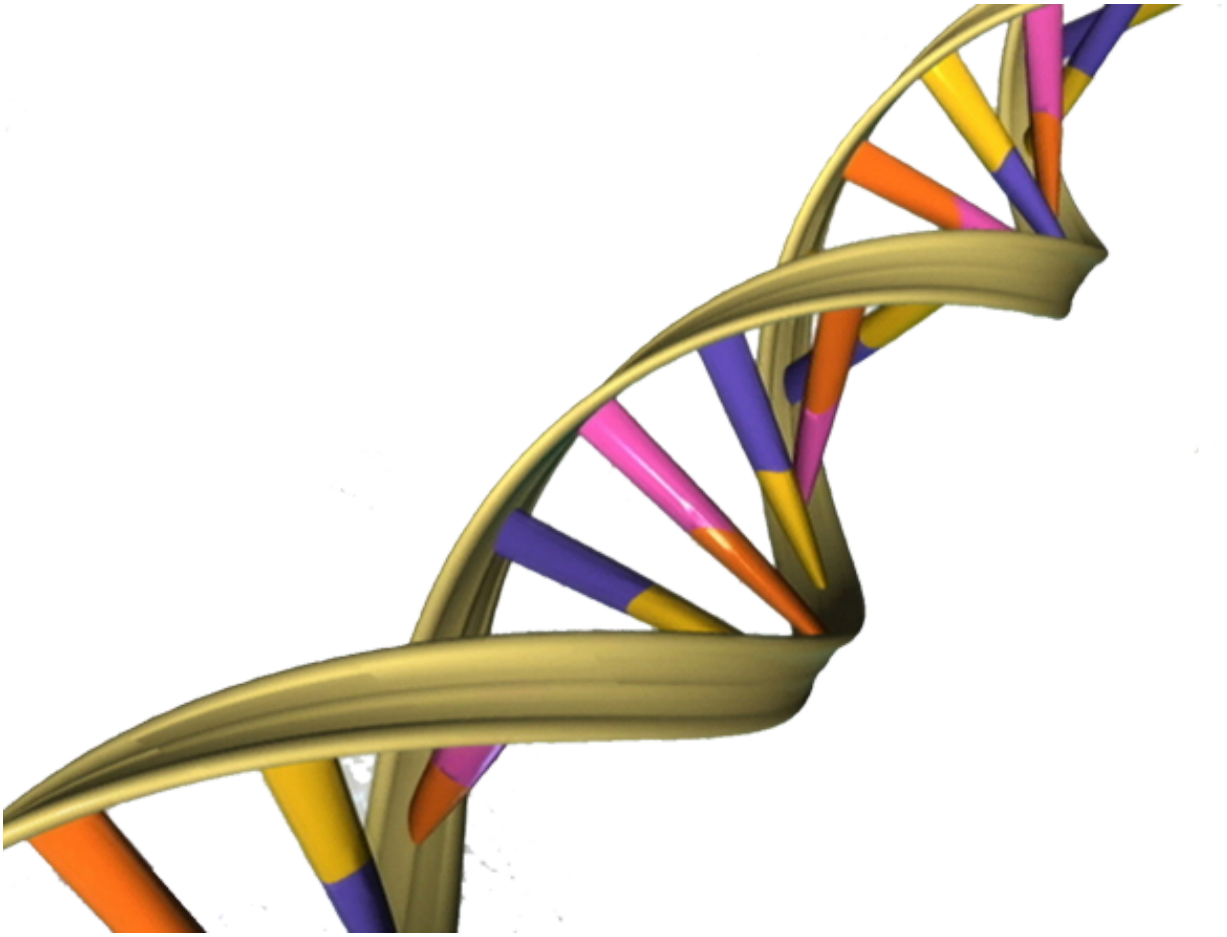

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Pediatric oncology researchers have pinpointed a crucial change in a single DNA base that both predisposes children to an aggressive form of the childhood cancer neuroblastoma and makes the disease progress once tumors form.

The change in the LMO1 gene results in a "super-enhancer," driving abnormally increased biological activity in the gene, resulting in tumor formation and progression. Although this discovery does not lend itself to immediate treatments for this high-risk subtype of neuroblastoma, greater understanding of these precise molecular events may potentially yield novel therapies.

"Cancers in general, and neuroblastoma in particular, have complex origins," said senior author John M. Maris, M.D., a pediatric oncologist at The Children's Hospital of Philadelphia (CHOP). "It's not common to discover causal gene variants in cancer, especially in a single base within the DNA sequence such as this." A change in a single base of DNA is called a single-nucleotide polymorphisms, or SNP.

The study appeared online today in *Nature*.

A cancer of the peripheral nervous system that usually occurs as a solid tumor in a child's chest or abdomen, neuroblastoma is the most common cancer in infants. It accounts for a disproportionate share of cancer deaths in children.

Maris and colleagues, including co-first authors Derek A. Oldridge, an M.D.-Ph.D. candidate, and Dr. Andrew Wood, an assistant professor at the University of Auckland in New Zealand, built on a 2011 genome-wide association study published in Nature by Maris's team. That research showed that common SNPs within the LMO1 gene drive neuroblastoma susceptibility and progression by abnormally altering gene transcription, part of the process by which DNA-encoded

information carries out biological functions. The new study sought to identify the precise variant in the DNA and to learn the molecular mechanisms set in motion by that change.

By mapping how DNA interacts with regulatory proteins that control transcription, the researchers narrowed down the culprit to the location where a single DNA base, guanine, drives super-enhancer activity, boosting LMO1 gene expression and causing tumors to arise and grow out of control.

The researchers also found that another genetic change has a beneficial effect: if the DNA base at the specified location is a different letter of the genetic alphabet, thymine instead of guanine, it protects against neuroblastoma. Gene studies in human populations suggest that this protective gene variant evolved after human ancestors migrated out of Africa, hundreds of thousands of years ago.

Over the years, researchers at CHOP have discovered a variety of genes contributing to neuroblastoma, and continue to pursue innovative therapies for high-risk, aggressive subtypes of the complex disease.

No existing drugs are known to inhibit the specific proteins that function abnormally in LMO1-driven neuroblastoma. However, adds Maris, other components on this biological pathway may offer attractive treatment targets: "Drugs that inhibit other parts of the gene transcription machinery may offer potential novel treatments for this aggressive subset of neuroblastoma." Further research at CHOP will pursue that strategy.

Oldridge's research on the super-enhancer was recognized last month by the International Society of Paediatric Oncology, which presented him with 30th annual Schweisguth Prize, awarded to the best scientific article by a trainee in pediatric oncology.

More information: Derek A. Oldridge et al. Genetic predisposition to neuroblastoma mediated by a LMO1 super-enhancer polymorphism, *Nature* (2015). DOI: 10.1038/nature15540

Provided by Children's Hospital of Philadelphia

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