

Researchers find gene location that gives rise to neuroblastoma, an aggressive childhood cancer

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Using advanced gene-hunting technology, an international team of researchers has for the first time identified a chromosome region that is the source of genetic events that give rise to neuroblastoma, an often fatal childhood cancer.

The investigators found that the presence of common DNA variations in a region of chromosome 6 raises the risk that a child will develop a particularly aggressive form of neuroblastoma, a cancer of the peripheral nervous system that usually appears as a solid tumor in the chest or abdomen. Neuroblastoma accounts for 7 percent of all childhood cancers, but due to its aggressive nature, causes 15 percent of all childhood cancer deaths.

“Until now we had very few clues as to what causes neuroblastoma,” said pediatric oncologist John M. Maris, M.D., who led the study at The Children’s Hospital of Philadelphia, where he is the director of the Center for Childhood Cancer Research. “Although there is much work to be done,” added Maris, “understanding this cancer’s origin provides a starting point for developing novel treatments.” The study team reported its findings in today’s Online First version of the New England Journal of Medicine.

Neuroblastoma is the most common solid cancer of early childhood and has long been known to include subtypes that behave very differently.

Some cases strike infants but spontaneously disappear with minimal treatment, while other cases in older children may be relentlessly aggressive from the start.

Researchers at Children's Hospital and colleagues in the multicenter Children's Oncology Group have for decades analyzed tumors for characteristics such as amplified levels of a cancer-causing gene and deletions of chromosome material. They used those tumor peculiarities to classify neuroblastoma into risk levels that guide oncologists toward the most appropriate treatments. "Properly defining risk level helps us to avoid the twin pitfalls of undertreating or overtreating any given child with neuroblastoma," added Maris.

However, little was known about genetic events that predispose a child to developing a neuroblastoma tumor. In roughly half of neuroblastoma cases, the cancer is not discovered until it has spread widely in a patient's body, so understanding how a tumor originates may allow oncologists to design earlier and more successful interventions.

In the current study, Maris's team collaborated with Hakon Hakonarson, M.D., Ph.D., director of Children's Hospital's Center for Applied Genomics, to analyze blood samples from approximately 1,000 neuroblastoma patients, as well as samples from some 2,000 healthy children recruited through the Children's Hospital network. A DNA chip analysis performed at the genome center identified three single nucleotide polymorphisms (SNPs)—changes in single bases on the DNA helix. Out of over 550,000 SNPs studied, those SNPs were much more common in patients with neuroblastoma, compared to the controls. The three SNPs occurred together on a band of chromosome 6 designated 6p22.

The researchers repeated the analysis in blood samples from additional groups of patients and control subjects from the U.S. and the U.K., and

confirmed their finding that variants in the 6p22 region were implicated in neuroblastoma. There are two genes in the 6p22 region, but their functions are largely unknown.

“We are doing further studies to understand how these relatively common genetic changes translate into increased risk of cancer,” said Maris. “Ultimately, they probably cause subtle changes in gene expression during early development, interacting with other genes yet to be discovered. This suggests that neuroblastoma has complex causes, in which a series of genetic changes may occur at different sites to combine into a ‘perfect storm’ that results in this cancer.”

The researchers found that patients with these at-risk SNPs on chromosome 6 were more likely to develop aggressive neuroblastoma. The initial changes on chromosome 6 in all their body cells eventually led to the genetic abnormalities seen in tumor cells in high-risk forms of the disease.

Because their finding reveals only the first step in a series of molecular events, added Maris, it would be premature to do prenatal genetic testing for the SNPs on chromosome 6. His research team will continue to perform genetic analyses, in search of other gene changes that interact with those SNPs. One data source will be 5,000 tissue samples in Maris’s lab—the world’s largest collection of neuroblastoma samples, drawing on decades of research into the disease by Maris, his colleagues and predecessors at Children’s Hospital.

“This discovery lays the foundation for learning how these initial changes influence biological pathways that lead to neuroblastoma,” added Maris. “Understanding those pathways may guide us to new and better therapies that precisely target this cancer.” Hakonarson added, “This study represents one of many ongoing projects to which scientists at The Children’s Hospital of Philadelphia are committed, and we

anticipate several comparable discoveries will be made in other common and equally complex pediatric disorders, such as autism, asthma, ADHD and diabetes.”

Source: Children's Hospital of Philadelphia

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