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Gene findings revealing reasons for neuroblastoma risk

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Two new studies from The Children's Hospital of Philadelphia advance the search for genetic events that result in neuroblastoma, a puzzling, often-deadly type of childhood cancer.

Originating in the peripheral nervous system, neuroblastoma is the most common solid cancer of early childhood and causes 15 percent of all childhood cancer deaths.

"Only two years ago we had very little idea of what causes neuroblastoma," said study leader John M. Maris, M.D., chief of Oncology and director of the Cancer Center at The Children's Hospital of Philadelphia. "Now we have unlocked a lot of the mystery of why neuroblastoma arises in some children and not in others."

In the largest gene study to date in pediatric oncology, Maris's study team performed a genome-wide association study to discover that common variants in the gene BARD1 increase a child's susceptibility to a high-risk form of neuroblastoma.

A second genome-wide study found that a copy number variation (CNV)—a missing stretch of DNA—along a structurally weak location on chromosome 1 plays an important role in the development of neuroblastoma. Although CNVs have received much attention from genetics researchers over the last several years, this study was the first example of a specific CNV that predisposes people to cancer.

The BARD1 study was published online in *Nature Genetics* on May 3, while the CNV study appears in tomorrow's issue of *Nature*. The researchers made use of highly automated gene-analyzing technology at the Center for Applied Genomics at Children's Hospital, directed by Hakon Hakonarson, M.D., Ph.D., a co-author of both studies. They used specimens collected from around the world through the Children's Oncology Group.

The BARD1 gene had already attracted attention from oncology researchers because it is associated with the gene BRCA1, which was the first discovered familial breast cancer gene. "Researchers have suspected that variants in BARD1 also increased the risk of breast cancer, but no one has found compelling evidence of this," said Maris. "Instead, surprisingly, our genome-wide association studies found that BARD1 is a susceptibility gene for neuroblastoma, and perhaps other cancers as well."

Maris added that researchers are now working to understand the mechanism by which BARD1 gene variants act on developing nervous system cells to give rise to cancer during fetal or early childhood development.

Maris's second study, spearheaded by Dr. Sharon Diskin, also of The Children's Hospital of Philadelphia, found that an inherited CNV located at chromosome 1q21.1 is associated with neuroblastoma. The chromosome region contains a large family of genes that are involved in the development of the nervous system, and the CNV they discovered changes how much of one particular gene is made within normal nerve and neuroblastoma cells.

This study, Maris added, opens up a new area for studying the mechanisms of how CNVs may increase the risk of cancer.

The current findings build on 2008 studies by Maris's lab, one identifying the ALK gene as the major gene predisposing patients to the rare familial form of neuroblastoma, and the other identifying a region of chromosome 6 that increases the risk of the nonhereditary form of the disease. The ALK gene discovery has already led to a clinical trial led by Dr. Yael Mosse of The Children's Hospital of Philadelphia.

As gene studies continue to better define the genetic landscape of neuroblastoma, added Maris, pediatric oncologists can better develop more precise targeted treatments to improve survival and quality of life for children with this complex disease. The Cancer Center at Children's Hospital has one of the nation's largest research and clinical programs in pediatric oncology.

Source: Children's Hospital of Philadelphia (news : web)