MedicalXpress

New gene variants raise risk of neuroblastoma, influence tumor progression

September 4 2012

Researchers have discovered two gene variants that raise the risk of the pediatric cancer neuroblastoma. Using automated technology to perform genome-wide association studies on DNA from thousands of subjects, the study broadens understanding of how gene changes may make a child susceptible to this early childhood cancer, as well as causing a tumor to progress.

"We discovered common variants in the HACE1 and LIN28B genes that increase the risk of developing neuroblastoma. For LIN28B, these variants also appear to contribute to the tumor's progression once it forms," said first author Sharon J. Diskin, Ph.D., a pediatric cancer researcher at The Children's Hospital of Philadelphia. "HACE1 and LIN28B are both known cancer-related genes, but this is the first study to link them to neuroblastoma."

Diskin and colleagues, including senior author John M. Maris, M.D., director of the Center for Childhood Cancer Research at Children's Hospital, published the study online Sept. 2 in *Nature Genetics*.

Striking the peripheral nervous system, neuroblastoma usually appears as a solid tumor in the chest or abdomen. It accounts for 7 percent of all childhood cancers, and 10 to 15 percent of all childhood cancer deaths.

The study team performed a genome-wide association study (GWAS), comparing DNA from 2,800 neuroblastoma patients with that of nearly 7,500 healthy children. They found two common gene variants

associated with neuroblastoma, both in the 6q16 region of chromosome 6. One variant is within the HACE1 gene, the other in the LIN28B gene. They exert opposite effects: HACE1 functions as a tumor suppressor gene, hindering cancer, while LIN28B is an oncogene, driving cancer development.

The current study showed that low expression of HACE1, a tumor suppressor gene, and high expression of LIN28B, an oncogene, correlated with worse patient survival. To further investigate the gene's role, the researchers used genetic tools to decrease LIN28B's activity, and showed that this inhibited the growth of neuroblastoma cells in culture.

The new research builds on previous GWAS work by Children's Hospital investigators implicating other common gene variants as neuroblastoma oncogenes. As in the current study, these gene variants show a double-barreled effect, both initiating cancer and provoking its progression.

"In addition to broadening our understanding of the heritable component of neuroblastoma susceptibility, we think this research may suggest new therapies," Diskin added. "Our follow-up studies will focus on how we may intervene on these genes' biological pathways to develop more effective treatments."

More information: "Common variation at 6q16 within HACE1 and LIN28B influence susceptibility to neuroblastoma," *Nature Genetics*, advance online publication, Sept. 2, 2012. doi:10.1038/ng.2387

Provided by Children's Hospital of Philadelphia