Medical Xpress

New gene variants increase risk of paediatric cancer

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Two new gene variants have been discovered by researchers from Italy and the United States that increase the risk of neuroblastoma, a paediatric cancer. This discovery was made using automated technology

to perform genome-wide association studies (GWAS) on DNA from thousands of subjects. The study has effectively broadened our understanding of how gene changes may make a child susceptible to this early childhood cancer, as well as causing a tumour to progress.

Neuroblastoma is a long-term debilitating and life-threatening disease that is associated with poor long-term survival and affects approximately 0.18 in 10,000 people in the European Union, the equivalent of around 9,100 people. It is the most common solid tumour outside the brain in children; symptoms may include weakness, bone pain, loss of appetite and fever. In many cases it is present at birth but is diagnosed later when the cancer has spread to other parts of the body and the child begins to show symptoms of the disease.

'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 tumour's progression once it forms,' said lead author Sharon J. Diskin, Ph.D., a paediatric 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 in Nature Genetics. Neuroblastoma strikes the peripheral nervous system and usually appears as a solid tumour in the chest or abdomen. It accounts for 7 % of all childhood cancers, and 10 to 15 % of all childhood cancer deaths.

The research team performed a GWAS, and compared 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 tumour suppressor gene, hindering cancer, while LIN28B is an oncogene, driving cancer development.

The study showed that low expression of HACE1 and high expression of LIN28B 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 work and 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.'

Currently in the EU, several medicines exist and are authorised for the treatment of neuroblastoma. Treatments for neuroblastoma include surgery, chemotherapy (medicines to treat cancer) and radiotherapy (treatment with radiation).

More information: Diskin, S.J., et al. 'Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma', *Nature Genetics*, 2012. doi: 10.1038/ng.2387

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