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Genome code cracked for most common form of pediatric brain cancer

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Scientists at the Johns Hopkins Kimmel Cancer Center have deciphered the genetic code for medulloblastoma, the most common pediatric brain cancer and a leading killer of children with cancer. The genetic "map" is believed to be the first reported of a pediatric cancer genome and is published online in the December 16 issue of *Science Express.*

Notably, the findings show that children with medulloblastoma have five- to tenfold fewer cancer-linked alterations in their genomes compared with their adult counterparts, the scientists say.

"These analyses clearly show that genetic changes in pediatric cancers are remarkably different from adult tumors. With fewer alterations, the hope is that it may be easier to use the information to develop new therapies for them," says Victor Velculescu, M.D., Ph.D., associate professor of oncology at the Johns Hopkins Kimmel Cancer Center.

"We now know what many pieces of the medulloblastoma puzzle are," adds Bert Vogelstein, M.D., Clayton Professor of Oncology and co-director of the Ludwig Center at Johns Hopkins. "Now, we must figure out how to put the puzzle together and zero in on parts of the puzzle to develop new therapies. This is what scientists will be focused on for the next decade."

The Johns Hopkins team used automated tools to sequence hundreds of millions of individual chemicals called nucleotides, which pair together in a preprogrammed fashion to build DNA and, in turn, a genome.

Combinations of these nucleotide letters form genes, which provide instructions that guide cell activity. Alterations in the nucleotides, called mutations, can create coding errors that transform a normal cell into a cancerous one. The scientists at Johns Hopkins have previously mapped genome sequences for pancreatic, adult brain, breast and colon cancers with similar methods.

For the study, scientists sequenced nearly all protein-encoding genes in 22 samples of pediatric medulloblastoma and compared these sequences with normal DNA from each patient to identify tumor-specific changes or mutations. Each tumor sample had an average of 11 mutations. There were 225 mutations in all.

Then, the investigators searched through a second set of 66 medulloblastomas, including some samples from adults, to find how these mutations altered the proteins made by the genes.

The team found that most of the mutations congregate within a few gene families or pathways. The most prevalent pathway ordered the way long strands of DNA, that make up chromosomes, are twisted and shaped into dense packets that open and close depending on when genes need to be activated. Such a process is regulated by chemicals that operate outside of genes, termed "epigenetic" by scientists.

Within the epigenetic pathway, two commonly mutated genes were both involved in how molecules called histones wrap around DNA.

"These epigenetic changes may be more important than we thought in childhood cancers," says Will Parsons, M.D., Ph.D., formerly of Johns Hopkins and now an assistant professor at Texas Children's Cancer Center and Baylor College of Medicine.

Mutations in MLL2 and MLL3 were identified in 16 percent of the

entire set of 88 medulloblastoma samples. Add to this three other epigenetic alterations found by the scientists in the genome scan, and the total set accounts for 20 percent of mutations in all the brain cancer samples.

Second to epigenetic pathways were gene mutations in pathways such as Hedgehog and Wnt that control tissue and organ development in humans and other animals. Both pathways have previously been linked to childhood medulloblastoma.

Cancer is the leading cause of death by disease in children in the U.S., and more children die of brain tumors than any other type of cancer. Medulloblastoma is the most common malignant brain tumor in children, occurring in about 400 children per year in the U.S.

"It's a particular challenge to treat children with brain cancer," says Parsons, "because our most effective treatments, surgery and radiation therapy, can cause significant side effects, including cognitive disabilities and hormone abnormalities. For our youngest patients, the effects can be potentially devastating."

Yet, Parsons is encouraged by the study's findings. "As oncologists, we're working to understand how specific genetic changes found in patients' cancers should guide their treatment. Any information that allows us to understand a patient's prognosis or provides clues about therapies that might work best in a patient is crucial and will help us provide better care."

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