Genomic study of rare children's cancer yields possible prognostic tool

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A new study of the genetic makeup, or genome, of Ewing sarcoma, a rare cancer that strikes children, teenagers, and young adults, has produced multiple discoveries: a previously unknown sarcoma subtype, genetic factors related to long-term survival, and identification of a genetic change between the primary and metastatic stages of the disease that could lead to better, more targeted treatment.

Researchers from Huntsman Cancer Institute (HCI) at the University of Utah used a new, advanced technology called molecular inversion probes (MIPs) to analyze DNA changes in the genome of Ewing sarcoma tumors. The report appears today in the online issue of the journal Cancer Genetics.

New Subtype of Ewing Sarcoma

According to the study's principal investigator, Joshua Schiffman, M.D., associate professor of pediatrics at the University of Utah and an HCI investigator, up to 10 percent of the tumor samples revealed that DNA in a specific region of the genome was missing, including a gene called SMARCB1. The same deletion had been described before in another aggressive and deadly sarcoma called a rhabdoid tumor. Pathologists double-checked the diagnosis on these samples and determined that they were not misdiagnosed rhabdoid tumors, but were indeed Ewing sarcoma that also had this rhabdoid characteristic.

"Discovering this new subset of Ewing sarcoma is especially important because the patients with this deletion were among the long-term survivors," said Schiffman. "It opens up questions about the biology of this tumor and whether patients with this type of cancer need different treatment."

Genome Factors Correlate with Long-Term Survival

The researchers also looked at the relationship between the Ewing sarcoma genome and patient outcomes and found factors in eight areas of the genome correlated in varying degrees with long-term survival after diagnosis. They compared the samples that contained none of these factors to those with one or more. Outcomes for the patients with none of the factors were considerably better: 80 percent of them had no recurrence of the disease after initial treatment, and even more outstanding, 100 percent survived more than 12 years after diagnosis. For patients with one or more of the factors, only about 40 percent survived that long.

"Our results will have to be validated with a larger number of samples, but MIPs give us the tool to do that on clinically archived samples," said Schiffman. "Clearly, learning more about cancers with these genomic factors will be essential to finding new treatments that will improve overall survival among all Ewing sarcoma patients."

Gene Difference in Metastatic Ewing Sarcoma Cells

The current model for how cancer spreads, or metastasizes, in the body holds that primary tumors change in some way that allows the cancer cells to spin off and move to other parts of the body. The researchers compared the DNA differences between primary tumor (the initial location of the cancer) cells, metastasized cells, and normal cells in the

same patients.

"We found a specific gene that was present only in the metastatic tumors and not the primary tumor or normal cells," said Schiffman. "That gene has been described before in relation to other types of cancers, but not Ewing sarcoma.

"People don't die from a primary tumor," he added. "It's cancer metastasizing and spreading through the body that kills. As we learn what makes tumors metastatic, we can search for treatments that may keep primary tumors from making that change or target this specific change once it already has occurred in metastatic tumors."

Use of Archived Tumor Samples

Only 300 to 400 new Ewing sarcoma cases are diagnosed per year in the United States. "The rarity of Ewing sarcoma poses a problem for cancer research," said Schiffman. "Because there are so few cases, it has been difficult in the past to find enough tissue samples to conduct valid studies of the genetics and biology of this disease."

Unlike other genetic analysis techniques, MIPs give very high quality, genome-wide, high-resolution DNA analysis for clinical samples that have been preserved in formalin and encased in paraffin wax blocks, a process called FFPE. "FFPE has been the standard technique for preserving pathology samples for decades," said Schiffman. "But until recently, genomics technology has not been available to make use of the huge resource these samples represent."

"We analyzed FFPE samples of primary tumors from Ewing sarcoma patients at Primary Children's Medical Center in Salt Lake City from the past 12 years. This doesn't sound like a large sample, but for this rare cancer it reflects 10 percent of all cases diagnosed in a given year, so the

quantity is significant," he added.

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