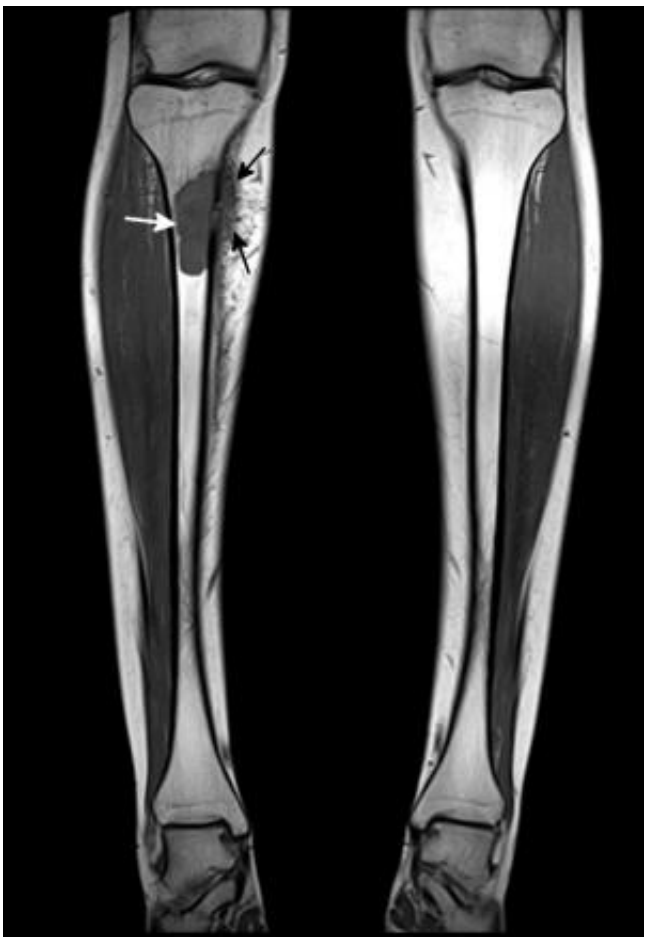
Gene sequencing projects link two mutations to Ewing sarcoma subtype with poor prognosis

November 12 2014



This Ewing sarcoma tumor in this MRI image of the lower extremities involves the right tibia bone (white arrow) and is associated with a soft tissue mass (black arrows). Credit: Drs. Navid, Coleman, Hillenbrand/St. Jude Children's Research Hospital

An international collaboration has identified frequent mutations in two genes that often occur together in Ewing sarcoma (EWS) and that define a subtype of the cancer associated with reduced survival. The research, conducted by the St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project and the Institut Curie-Inserm through the International Cancer Genome Consortium, appears in the current issue of the scientific journal *Cancer Discovery*.

Mutations in the genes STAG2 and TP53 have previously been linked to EWS. This is the first study to show that patients whose tumors carry alterations in both genes are less likely to survive than are patients without the changes. The discovery stems from the most comprehensive analysis yet of the genetic makeup of EWS, a cancer of the bone and soft tissue that primarily strikes children and adolescents.

The findings come as St. Jude finalizes plans for clinical trials of EWS combination therapy. A recent St. Jude study showed combination therapy was effective in mice with EWS that included both mutations. The agents work by damaging DNA or interfering with cellular repair mechanisms.

"The current study used whole-genome sequencing to define the most comprehensive landscape yet of the genetic alterations that contribute to the growth and recurrence of Ewing sarcoma," said Jinghui Zhang, Ph.D., a member of the St. Jude Department of Computational Biology. Zhang and Olivier Delattre, M.D., Ph.D., head of the genetic and biology of pediatric cancer group of Institut Curie, Paris, are the study's corresponding authors.

"With the combined expertise of St. Jude and Institut Curie, we were able to identify a subtype with a dismal prognosis based on a tumor's genetic profile. This is an important step in developing more effective diagnosis and treatment," Zhang said.

The study involved sequencing the complete normal and cancer genomes of 112 EWS patients, including children, teenagers and young adults. The genome is encoded in the DNA molecule carried in almost every cell and carries the instructions needed to assemble and sustain life.

"The Institut Curie is a reference center in France for Ewing sarcoma. Twenty-two years ago, my team identified the EWSR1-FLI1 gene fusion, a pathogenomonic marker and a key pathogenic event in this disease. Thanks to this French-U.S. collaboration, we now have a more complete picture of the different genetic abnormalities that can be associated with EWSR1- FLI1 and may hence contribute to its aggressiveness. Hopefully, this may lead to improve treatment strategies," Delattre said.

EWS is identified in about 250 children and adolescents annually in the U.S., making it the second most common pediatric bone tumor. With current therapies, 75 to 80 percent of patients whose disease has not spread will become long-term survivors. But the prognosis is bleak for other patients.

Nearly all EWS begins with a chromosomal rearrangement that fuses part of the EWSR1 gene with a segment of FLI1 or a related gene. The fusion leads to production of an abnormal protein, which disrupts regulation of genes involved in cell growth and survival.

This study focused on identifying the genetic changes that follow the chromosomal rearrangement and help drive tumor formation.

"Identifying these changes using whole-genome sequencing and understanding how they alter survival can be critical to developing more effective treatments," said co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis.

Whole genome sequencing revealed that unlike adult cancers, EWS is characterized by relatively few mutations. The most commonly altered gene identified in this study was STAG2, which was mutated in 17 percent of the 112 tumors sequenced. The tumor suppressor gene TP53 was mutated in 7 percent of the tumors.

When researchers checked for the alterations in 299 French EWS patients, they found that STAG2 and TP53 mutations often occurred together and were associated with poor outcomes. Patients whose tumors include both mutations were far less likely than patients with neither mutation to be alive five years after their cancer was discovered. Mutations in either STAG2 or TP53 alone were not associated with a significantly worse outcome.

TP53 is the most frequently altered gene in human cancer. STAG2 mutations have been identified in a variety of cancers, including the brain tumor glioblastoma, the skin cancer melanoma and bladder cancer. In this study, the mutations inactivated the STAG2 gene. The gene carries instructions for assembling the STAG2 protein, which is part of a protein complex that ensures chromosomes separate normally during cell division.

St. Jude researchers recently identified a promising three-drug combination therapy for EWS with STAG2 and TP53 mutations. The treatment combines the chemotherapy drugs irinotecan and temozolomide, which are already used to treat EWS, with investigational drugs called PARP inhibitors. EWS disappeared and did not return in more than 70 percent of mice treated with the combination therapy.

Clinical trials of the combination therapies for treatment of EWS are expected to open later this year at St. Jude and Dana-Farber/Harvard Cancer Center in Boston. The trials will involve EWS patients whose cancer remained following standard therapy or has returned.

In the current study, researchers detailed other insights regarding the role of STAG2 mutations in EWS. The findings included evidence the mutation was associated with relapse in several patients.

While STAG2 and TP53 mutations frequently occurred together in EWS, researchers found that mutations in STAG2 and the CDKN2A gene were usually mutually exclusive. CDKN2A carries instructions for making proteins that regulate cell division. Mutations in CDKN2A have been reported in EWS and other cancers, but this is the first study to recognize that CDKN2A and STAG2 mutations rarely occur together in EWS. The finding provides important insight into the tumor's genetic profile, which will aid efforts to develop more effective therapies.

Provided by St. Jude Children's Research Hospital