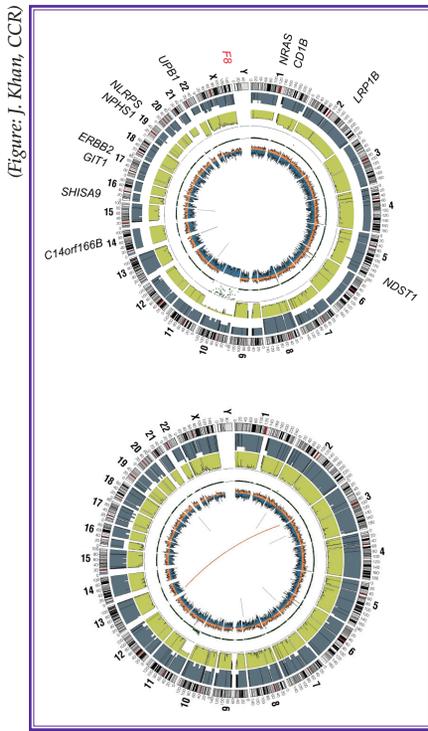


Seeing the Forest and the Trees

Comprehensive genomic analysis gives new insight into a highly malignant childhood tumor.



(Figure: J. Khan, CCR)

Circos plots of genomic alterations in two of the 147 rhabdomyosarcomas examined for this study.

As little as 15 years ago, sequencing a human genome required the cooperation of multiple research centers and millions of dollars. Today the time and costs associated with genomic analysis have plummeted by orders of magnitude, giving cancer researchers an unprecedented ability to examine entire tumor genomes for changes that may drive disease.

Javed Khan, M.D., Deputy Chief of CCR's Genetics Branch and an Investigator in CCR's Pediatric Oncology Branch, and his Clinical Fellow, Jack Shern, M.D., have taken this survey approach to the childhood cancer, rhabdomyosarcoma. Rhabdomyosarcoma, the most common soft-tissue sarcoma in children, is still relatively rare, affecting 350 patients per year. While many patients are successfully treated with existing therapeutic regimens, some go on

to develop metastatic disease and have a five-year survival rate of only 30 percent.

Khan, Shern, and their colleagues studied 147 tumors and compared them with matched control tissue. They used a combination of whole-genome sequencing (WGS), whole-exome sequencing (WES), and whole-transcriptome sequencing (WTS), along with high-resolution single-nucleotide polymorphism (SNP) arrays, to provide a comprehensive genomic landscape for this disease. The results were published in the February 1, 2014, issue of *Cancer Discovery*.

The researchers found two broad classes of tumors separable by the presence or absence of a novel gene resulting from the fusion of *PAX3* or *PAX7* with the *FOXO1* gene on a different chromosome. This fusion leads to altered expression of many genes because it acts as an aberrant transcription factor. The presence of a fusion gene was associated with very few additional genetic alterations (usually an amplification or deletion), and with poor clinical outcomes. Absence of the fusion gene was associated with a broader collection of genomic abnormalities including chromosomal rearrangements, aneuploidies, and mutations. Many previously identified genes were implicated, as well as some new suspects like *FBXW7* and *BCOR*. Tumors lacking the PAX fusion gene expressed mutations in genes that were induced or suppressed by the PAX fusion gene.

Recurrence of alterations to the same gene in multiple tumors suggests it may be central to the disease process. Because this cancer has a relatively low mutation rate, the team was faced with assigning

significance to genetic alterations in potentially interesting signaling molecules, which could be found in a few, or even only one, tumor samples. However, when they analyzed the context of these rare and singleton mutations, they discovered that many were part of the same signaling pathways. In particular, they found alterations in the receptor tyrosine kinase/RAS/PIK3CA signaling pathways in 93 percent of the tumors.

Khan and Shern are continuing their work with the Children's Oncology Group, which has identified an additional 650 clinically annotated samples to enable follow up work on the genes identified in this study. "I think we've described the tip of the iceberg. In the next couple of years, we'll hopefully be able to associate prognosis and therapies based on the particular mutations we find," said Shern.

Building on this research, the team also plans to design and test interventions that target the genetic drivers they have identified.

"These studies are very difficult to do because tissue acquisition and validation is so complex," said Khan. "This work would not have been possible without our brave pediatric patients and their families. In the face of their life-threatening disease, they offered their tumors for study knowing that they may not personally benefit from this work but in the hope that investigators might learn lessons that would help children diagnosed with rhabdomyosarcoma in the future."

To learn more about Dr. Khan's research, please visit his CCR website at <http://ccr.cancer.gov/staff/staff.asp?name=khan>.