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Researchers discover genetic cause of second-most common kidney cancer in children

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The genetic basis of clear cell sarcoma of the kidney (CCSK), a high-risk childhood cancer known for metastasizing to bone and brain, has remained a mystery since the cancer was first described in the 1970s. A team of researchers from Baylor College of Medicine and Texas Children's Hospital has now uncovered a genetic mutation associated with CCSK that has opened a new path of research and could point the way toward a new diagnostic test for the disease.

"The work is one of the first descriptions of a defining genetic hallmark in clear cell sarcoma of the kidney," said Dr. Angshumoy Roy, assistant professor of pathology & immunology at Baylor and Texas Children's Hospital and lead author of the study in *Nature Communications*.

The collaborative research team used a combination of whole exome sequencing and whole-transcriptome (RNA) sequencing to characterize the genomic landscape of CCSK. They initially detected a mutation in the BCOR gene, which is involved in regulating cell differentiation through epigenetic mechanisms, in a single patient with CCSK. Further investigation then led to the discovery of recurrent duplication mutations within the gene in 85 percent of CCSKs, but not in other childhood kidney tumors, such as Wilms tumors.

"The discovery of these duplications in the vast majority of CCSKs, but not in Wilms tumors, offers the potential for a highly sensitive and specific molecular diagnostic test for these cancers," said Dr. Will Parsons, associate professor of pediatrics at Baylor and co-director of

the Cancer Genetics and Genomics Program at Texas Children's Cancer Center and also an author of the paper.

The specific type of mutation identified in the tumors, called internal tandem duplications (ITDs), has only been rarely reported in cancers, possibly explained in part by the fact that they are difficult to detect through standard bioinformatics techniques. The researchers examined published data from a previous study on CCSKs and found identical ITDs in those tumors that had gone previously undetected, underscoring the need for specialized informatics tools to detect these mutations, Roy said.

A second discovery of this research was an unexpected link between CCSKs and undifferentiated sarcomas, which also have mutations involving the BCOR gene but apart from that, do not have similarities in natural history or clinical behavior.

"This highlights the importance of using unbiased genomic profiling as a tool to uncover biological similarities between tumors that may lead to the redesigning of therapeutic strategies," Parsons said.

Provided by Baylor College of Medicine