Comprehensive genomic analysis offers insights into causes of Wilms tumor development

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A comprehensive genomic analysis of Wilms tumor - the most common kidney cancer in children - found genetic mutations involving a large number of genes that fall into two major categories. These categories involve cellular processes that occur early in kidney development. The study, published in *Nature Genetics*, offers the possibility that targeting these processes, instead of single genes, may provide new opportunities

for treatment of Wilms tumor.

"It is very difficult to therapeutically target over 40 genes that may be mutated in Wilms tumor," said senior author Elizabeth Perlman, MD, from Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago. "We discovered that many of these genetic mutations converge into two developmental pathways that lead to cancer. Early development of the kidney starts with rapid proliferation of undifferentiated cells. Within these cells, a signal triggers a switch to undergo differentiation into the normal cells of the kidney. In Wilms tumors, one set of mutations promotes abnormal and continued proliferation of the undifferentiated cells. A second set of mutations impacts the differentiation switch itself. Targeting these two different pathways in future studies might be more efficient than targeting individual gene mutations."

Perlman is the Head of the Department of Pathology and Laboratory Medicine at Lurie Children's and a Professor of Pathology at Northwestern University Feinberg School of Medicine. She is the Arthur C. King Professor of Pathology and Laboratory Medicine.

In the study, Perlman and colleagues in the Children's Oncology Group and the National Cancer Institute initially identified all genetic mutations in 117 Wilms tumor cases. Then they focused on a set of genetic mutations that occurred in more than one case and conducted a targeted analysis of these recurrent mutations in 651 Wilms tumors to validate the results. They found that the most common genes mutated in Wilms tumor were TP53, CTNNB1, DROSHA, WT1 and FAM123B.

In an unexpected finding, Perlman and colleagues also identified underlying germline mutations - or mutations in all the cells of the body - in at least 10 percent of Wilms tumor cases. "Our discovery of germline mutations in so many cases of Wilms tumor means that the

children and family members of these patients may be at risk for tumor development," said Perlman.

More information: A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. *Nature Genetics* (2017). DOI: 10.1038/ng.3940

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