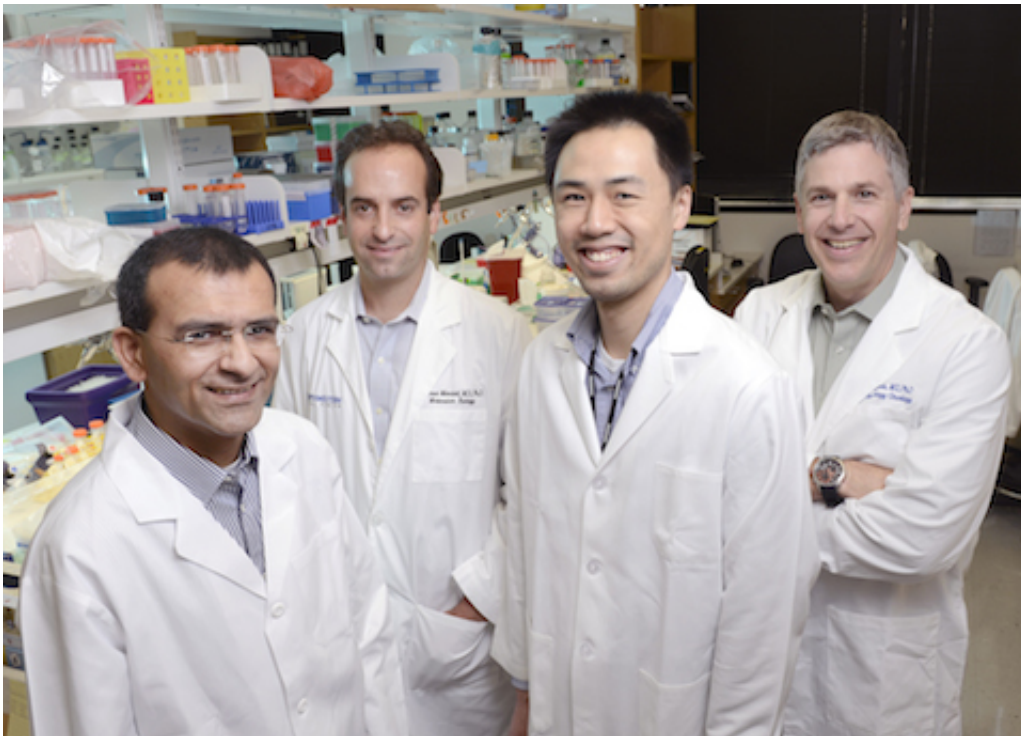


Researchers find new gene mutations for Wilms Tumor

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(l-r) Drs. Dinesh Rakheja, Joshua Mendell, Kenneth Chen, and James Amatruda.
Credit: UT Southwestern Medical Center

Researchers at UT Southwestern Medical Center and the Gill Center for Cancer and Blood Disorders at Children's Medical Center, Dallas, have made significant progress in defining new genetic causes of Wilms tumor, a type of kidney cancer found only in children.

Wilms [tumor](#) is the most common childhood genitourinary tract [cancer](#) and the third most common solid tumor of childhood.

"While most children with Wilms tumor are thankfully cured, those with more aggressive tumors do poorly, and we are increasingly concerned about the long-term adverse side effects of chemotherapy in Wilms tumor patients. We wanted to know – what are the genetic causes of Wilms tumor in children and what are the opportunities for targeted therapies? To answer these questions, you have to identify genes that are mutated in the cancer," said Dr. James Amatruda, Associate Professor of Pediatrics, Molecular Biology and Internal Medicine at UT Southwestern and senior author for the study.

The new findings appear in *Nature Communications*. Collaborating with Dr. Amatruda on the study were UT Southwestern faculty members Dr. Dinesh Rakheja, Associate Professor of Pathology and Pediatrics; Dr. Kenneth S. Chen, Assistant Instructor in Pediatrics; and Dr. Joshua T. Mendell, Professor of Molecular Biology. Dr. Jonathan Wickiser, Associate Professor in Pediatrics, and Dr. James Malter, Chair of Pathology, are also co-authors.

Previous research has identified one or two mutant genes in Wilms tumors, but only about one-third of Wilms tumors had these mutations.

"We wanted to know what genes were mutated in the other two-thirds. To accomplish this goal, we sequenced the DNA of 44 tumors and identified several new mutated genes," said Dr. Amatruda, who holds the Nearburg Family Professorship in Pediatric Oncology Research and is an Attending Physician in the Pauline Allen Gill Center for Cancer and Blood Disorders at Children's Medical Center. "The new genes had not been identified before. The most common, and in some ways the most biologically interesting, mutations were found in genes called DROSHA and DICER1. We found that these mutations affected the cell's

production of microRNAs, which are tiny RNA molecules that play big roles in controlling the growth of cells, and the primary effect was on a family of microRNAs called let-7."

"Let-7 is an important microRNA that slows cell growth and in Wilms tumors in which DROSHA or DICER1 were mutated, let-7 RNA is missing, which causes the cells to grow abnormally fast," Dr. Amatruda said.

These findings have implications for future treatment of Wilms tumor and several other childhood cancers, including neuroblastoma, germ cell tumor, and rhabdomyosarcoma.

"What's exciting about these results is that we can begin to understand what drives the growth of different types of Wilms tumors. This is a critical first step in trying to treat the cancer based on its true molecular defect, rather than just what a tumor looks like under a microscope," Dr. Amatruda said. "Most importantly, we begin to think in concrete terms about a therapy, which is an exciting translational goal of our work in the next few years. This study also is a gratifying example of great teamwork. As oncologists, Dr. Chen and I were able to make rapid progress by teaming up with Dr. Rakheja, an expert pathologist, and with Dr. Mendell, a leading expert on microRNA biology."

According to the American Cancer Society, an estimated 510 cases of Wilms tumor will be diagnosed among children in 2014. Also called nephroblastoma, Wilms tumor is an embryonal tumor of the kidney that usually occurs in children under age 5, and 92 percent of kidney tumors in this age group are Wilms tumor. Survival rates for Wilms tumor have increased from 75 percent in 1975-1979 to 90 percent in 2003-2009.

Provided by UT Southwestern Medical Center

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