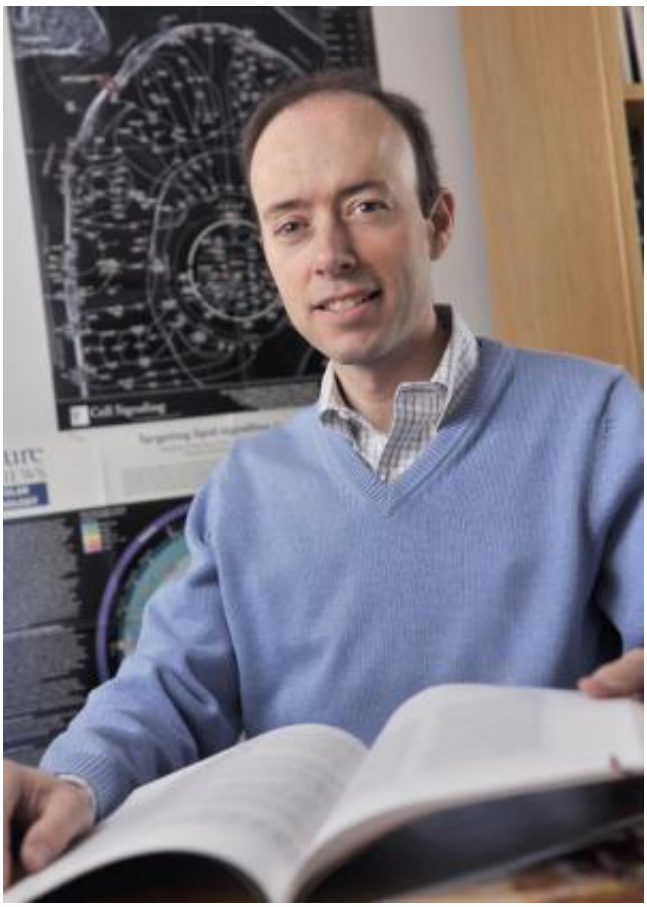
Medical Xpress

Cancer researchers identify gene mutations and process for how kidney tumors develop

November 17 2014



Dr. James Brugarolas, Associate Professor of Internal Medicine and Developmental Biology at UT Southwestern. Credit: UT Southwestern Medical Center

Using next generation gene sequencing techniques, cancer researchers at

UT Southwestern Medical Center have identified more than 3,000 new mutations involved in certain kidney cancers, findings that help explain the diversity of cancer behaviors.

"These studies, which were performed in collaboration with Genentech Inc., identify novel therapeutic targets and suggest that predisposition to kidney cancer across species may be explained, at least in part, by the location of tumor suppressor genes with respect to one another in the genome," said Dr. James Brugarolas, Associate Professor of Internal Medicine and Developmental Biology, who leads UT Southwestern's Kidney Cancer Program at the Harold C. Simmons Cancer Center.

The scientists' findings are outlined in separate reports in the *Proceedings of the National Academy of Sciences* and *Nature Genetics*.

More than 250,000 individuals worldwide are diagnosed with kidney cancer every year, with lifetime risk of kidney cancer in the US estimated at 1.6 percent. Most kidney tumors are renal cell carcinomas, which when metastatic remain largely incurable.

Researchers with UT Southwestern's Kidney Cancer Program had previously identified a critical gene called BAP1 that is intimately tied to kidney cancer formation. Their latest research shows how BAP1 interacts with a second gene, VHL, to transform a normal kidney cell into a cancer cell, which in part appears to be based on the two gene's close proximity in humans, said Dr. Brugarolas, a Virginia Murchison Linthicum Endowed Scholar in Medical Research.

The newest findings suggest that the transformation begins with a mutation in one of the two copies of VHL, which is the most frequently mutated gene in the most common form of kidney cancer, clear cell type, which accounts for about 75 percent of kidney cancers. The VHL mutation is followed by a loss of the corresponding chromosome arm

containing the second copy of VHL, as well as several other genes including PBRM1 and BAP1. This step eliminates the remaining copy of VHL and along with it, one of the two copies of PBRM1 and BAP1, two important genes that protect the kidney from cancer development. The subsequent mutation of the remaining copy of BAP1 leads to aggressive tumors, whereas mutation of the remaining copy of PBRM1 induces less aggressive tumors, said Dr. Payal Kapur, a key investigator of both studies who is an Associate Professor of Pathology and Urology, and the Pathology co-Leader of the Kidney Cancer Program.

This model also explains why humans born with a mutation in VHL have a high likelihood of developing kidney cancer during their life time. In these individuals, all kidney cells are already deficient for one VHL copy and a single deletion eliminates the second copy, along with a copy of BAP1 and PBRM1. In contrast, in other animals, these three genes are located on different chromosomes and thus more mutational events are required for their inactivation than in humans. Consistent with this notion, when UT Southwestern researchers mutated VHL and BAP1 together, kidney cancer resulted in animals.

In a second collaborative study with Genentech Inc., published in *Nature Genetics*, investigators implicated several genes for the first time in non-clear cell kidney cancer, a less common type that accounts for about 25 percent of kidney cancers. Researchers identified a gene signature that can help differentiate subtypes of non-clear cell tumors to better define their behavior. Specifically, the researchers characterized alterations from 167 human primary non-clear cell renal cell carcinomas, identifying 16 significantly mutated genes in non-clear cell kidney cancer that may pave the way for the development of novel therapies. The research team also identified a five-gene set that enabled molecular classifications of tumor subtypes, along with a potential therapeutic role for BIRC7 inhibitors for future study.

More information: Spectrum of diverse genomic alterations define non–clear cell renal carcinoma subtypes, *Nature Genetics*, DOI: 10.1038/ng.3146