

## GENETICS

## A molecular atlas of clear cell renal cell carcinoma

**C**lear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer, but the molecular pathogenesis of the disease remains poorly understood. Two recently published studies have sought to remedy this situation by analysing the genetic changes underlying the disease.

In a recent article in *Nature*, The Cancer Genome Atlas Research Network report their survey of over 400 tumours to identify significantly mutated genes. Using a number of different genomic platforms—including RNA sequencing, DNA methylation arrays, microRNA sequencing, single nucleotide polymorphism (SNP) arrays, reverse phase protein arrays and exome sequencing—the group identified 19 genes that were significantly mutated.

Such mutations commonly involved entire chromosome arms as opposed to focal events, most frequently arm-level events of chromosome 3p, the location of the four most commonly mutated genes in ccRCC: *VHL*, *PBRM1*, *BAP1* and *SETD2*. Arm-level mutations were also observed on chromosome 14q, which is associated with loss of *HIF1A*, a gene predicted to drive more-aggressive disease.

*BAP1* mutation was significantly correlated with poor survival, as were reduced AMPK and increased acetyl-CoA carboxylase protein levels, both of which contribute to a metabolic shift towards increased fatty acid synthesis. Overall, a metabolic shift towards a ‘Warburg-effect’ like state was noted, with downregulation of AMPK complex and Krebs cycle genes and upregulation of pentose phosphate pathway genes and fatty acid synthesis genes associated with poor prognosis.

The Cancer Genome Atlas group suggest that some of the identified genes could be targeted for future therapeutic options. “These findings, consistent with a Warburg metabolic shift in clear cell kidney cancer with poor survival, suggest that these tumours are dependent on aerobic glycolysis, impaired oxidative

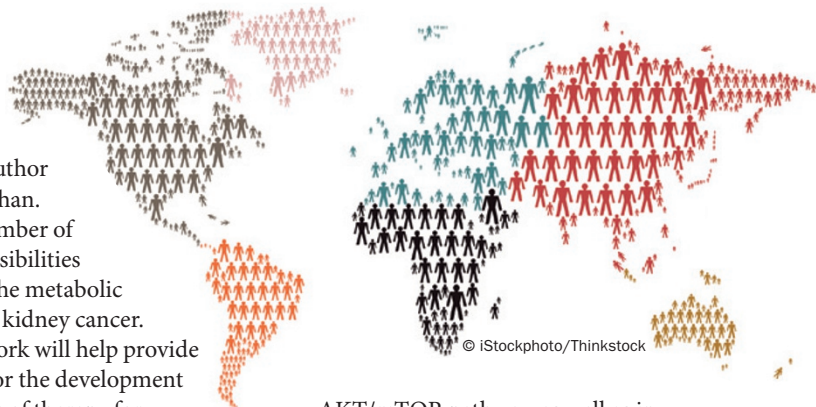
phosphorylation and increased fatty acid synthesis,” comments corresponding author W. Marston Linehan.

“This raises a number of very exciting possibilities about targeting the metabolic basis of clear cell kidney cancer. Hopefully this work will help provide the foundation for the development of effective forms of therapy for patients with this malignancy.”

Further to these exciting developments, a second paper, published in *Nature Genetics*, also reports the elucidation of the genetic background of ccRCC using a combination of whole-genome, exome and RNA sequencing, and array-based methylation, copy number and expression analyses. The researchers used an extended cohort of 204 ccRCC specimens, which were analysed to validate and clarify the effects of major genetic abnormalities.

Similar to the results reported by the Cancer Genome Atlas, Seishi Ogawa and colleagues observed recurrent mutations in targets on chromosome 3p, including *VHL*, *PBRM1*, *BAP1* and *SETD2*. 94% of samples exhibited loss of heterozygosity (LOH) at 3p, often caused by simple 3p loss. Most samples exhibiting LOH at 3p had the second *VHL* allele affected by somatic mutation or promoter methylation. Furthermore, the team found a novel mutation in the *VHL* pathway, in *TCEB1*, which encodes a vital part of the *VHL* complex. Overall, genetic and epigenetic lesions in the *VHL* complex accounted for 229 of the 240 specimens, in which *VHL* and *TCEB1* lesions were mutually exclusive, once again emphasizing the importance of *VHL* complex inactivation in ccRCC.

Echoing the data from The Cancer Genome Atlas, a large number of ccRCC cases involved mutations in the *PI3K/*



AKT/mTOR pathway, as well as in *TET2*, and *KEAP1*. *TET2* encodes an oxygenase that catalyses a critical step in DNA demethylation, whereas *KEAP1* is a component of a complex involved in oxidative stress responses.

The team also classified ccRCC cases into three subgroups based on DNA methylation patterns. Those with a high methylation subtype showed significantly worse prognosis, suggesting that patients with these tumours should be monitored for development of metastases for potential aggressive treatment.

The use of integrated molecular analysis in this study has enabled the researchers to piece together a deeper understanding of the interplay of genetic mechanisms affecting ccRCC pathogenesis. “Our study underscores the importance of integrated molecular studies to understand the pathogenesis of human cancers,” explains Ogawa. The team now plan to validate their findings in a larger cohort and to investigate the relationship between mutation status and specific treatment responses.

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**Original articles** The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* doi:10.1038/nature12222 | Sato, Y. et al. Integrated molecular analysis of clear-cell renal cell carcinoma. *Nat. Genet.* doi:10.1038/ng.2699