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Renal-cell carcinoma: a step closer to a new classification

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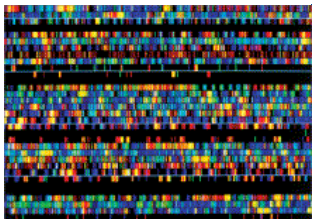
Until the advent of next-generation sequencing, somatic genetic changes common in sporadic renal-cell carcinoma were largely unknown. Mutations in the *VHL* gene, discovered by linkage analysis in hereditary renal-cell carcinoma, had been the focus of genetics research for many years for this type of cancer. Located on chromosome 3p, *VHL* is a tumour suppressor gene universally mutated in the hereditary form of clear-cell renal-cell carcinoma and in the vast majority of its sporadic form.[1] Previous studies[2], [3] measuring associations between *VHL* mutational status and clinical outcome did not detect a clear and consistent relation. Recent tumour sequencing studies have revealed several recurrent mutations in clear-cell renal-cell carcinoma in addition to *VHL*, including mutations in genes at the 3p locus. One such gene, *PBRM1*, has a truncating mutation in 40% of cases of clear-cell renal-cell carcinoma. *PBRM1* encodes the Baf180 protein, a subunit of the SWI/SNF chromatin remodelling complex implicated in the transcription machinery.[4] *BAP1*, also located at 3p, is mutated in 15% of clear-cell renal-cell carcinomas and encodes a protein implicated in deubiquitination, as part of the large ubiquitin-mediated proteolysis pathway (UMPP), a pathway that also includes *VHL* among about 135 genes. Alterations in genes encoding UMPP are associated with overexpression of hypoxia inducible factor, even in the absence of *VHL* mutation.[5]

Interestingly, *PBRM1* and *BAP1* mutations tend to be mutually exclusive, raising a potential genetic split that warrants investigation into the clinical implications. To that end, Payal Kapur and colleagues[6] followed on their initial report on *BAP1* loss to clinically characterise clear-cell renal-cell carcinoma tumours bearing mutations in either *PBRM1* or *BAP1*, or both. This work represents one of the strongest attempts in the next-generation sequencing era to integrate genomics with clinically relevant outcomes in renal-cell carcinoma. It builds on a local database (at the University of Texas-Southwestern, UTSW) and validates the findings in the publicly available database of The Cancer Genome Atlas (TCGA). The results showed that compared with *PBRM1*-mutant tumours, *BAP1*-mutant tumours are more likely to be aggressive and display adverse pathological features, which translate into striking overall survival differences. The hazard ratio for survival comparing patients with *BAP1*-mutant tumours with patients with *PBRM1*-mutant tumours was almost identical in both cohorts (2·7, 95% CI 0·99—7·6, p=0·044 for the UTSW cohort and 2·8, 1·4—5·9; p=0·004 for the TCGA cohort). Furthermore, *BAP1*-mutant and *PBRM1*-mutant tumours exhibited distinct gene-expression signatures indicating non-overlapping biology. Although the clinical utility of *PBRM1* and *BAP1* mutational status as biomarkers for renal-cell carcinoma might not be immediately applicable in daily clinical practice, these findings are a meaningful step.

Next, it will be important to test the predictive value of these mutations in patients receiving systemic therapies with targeted drugs such as inhibitors of VEGF and mTOR. Distinct genetics in renal-cell carcinoma might imply distinct responses to targeted agents. Seven therapies approved by the US Food and Drug Administration (FDA) were available in 2012. Rather than being used on the basis of a patient-restricted genetic signature, these drugs are currently prescribed on the basis of the eligibility criteria in pivotal phase 3 trials, patient preferences, toxicity profiles, and costs. Additionally, if *BAP1* and *PBRM1* mutations prove to be early events in tumorigenesis of clear-cell renal-cell carcinoma, ubiquitous throughout an individual's tumour, the recently raised issue of tumour heterogeneity in this disease becomes a lesser concern in the implementation of a biomarker based on mutational status.[7]



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Could we perceive other useful classifications from all the emerging data with the new candidate genes in clear-cell renal-cell carcinoma? Less common mutations are found in genes encoding two methyltransferases, *SETD2* and *MLL2*, and two demethylases, *UTX* (*KDM6A*) and *JARID1C* (*KDM5C*), and might define other molecular subtypes with different biology and outcomes. One potential classification scheme can involve the presence or absence of one or more mutations in a certain pathway. As previously mentioned, the UMPP groups several genes that target and degrade proteins through the proteasome system. One recent study[8] interrogated the genes of the UMPP and found that 48 (50%) of 98 patients with clear-cell renal-cell carcinoma harboured non-silent somatic mutations along that pathway, suggesting that patients with clear-cell real-cell carcinoma can be split into ones with mutations in the UMPP or not.

In summary, this well-designed study is an important first step in organising and understanding the clinical application of all the recent emerging data from efforts in exome sequencing of renal cancer. We hope that improved use of targeted therapies and biomarker-based clinical decisions will follow.[9]

We declare that we have no conflicts of interest.

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