KIDNEY CANCER

New genomic variation found

The first comprehensive genomic analysis comparing subtypes of nonclear cell renal carcinoma (nccRCC) has been published in *Nature Genetics*. The findings of this investigation have implications for the accurate presurgical diagnosis of distinct nccRCC tumour types and also provide new therapeutic targets for this disease.

nccRCC accounts for approximately 25% of renal cell carcinoma (RCC) diagnoses and is comprised of distinct tumour subtypes including papillary RCC (pRCC), chromophobe RCC (chRCC) and translocation RCC (tRCC). Identification of chRCC, in particular, is difficult as tumour features often overlap with those of benign renal oncocytoma.

Using next-generation sequencing technologies, Durinck *et al.* analysed exome, transcriptome and copy number alteration data from 167 primary human nccRCC tumour samples. Key amongst their findings was the identification of a set of five genes—*ASB1*, *GLYAT*, *PDZK1IP1*, *PLCG2* and *SDCBP2*—that enabled molecular classification of pRCC, chRCC and renal oncocytoma. Over 3,000 new mutations and 17 genes (most of which have not previously been reported) that might be involved in the pathogenesis of nccRCC were also discovered. In contrast to clear cell RCC (ccRCC) mutations in *VHL*, *TCEB1* and *BAP1* were absent, whereas mutations in tumour suppressor genes such as *SETD2* or *ARID1A* could be present in both ccRCC and nccRCC.

Exome sequencing revealed somatic protein-altering mutations in 2,364, 781 and 509 genes in pRCC, chRCC and renal oncocytoma, respectively. Comparing these observed changes with those that have been reported in the Catalogue of Somatic Mutations in Cancer revealed that 90% of them were new. Significantly more alterations on average per pRCC sample were observed than are identified in The Cancer Genome Atlas of ccRCC (61 compared with 45, respectively). In pRCC, 10 genes were found to be significantly mutated—*MET*, *SLC5A3*, *NF2*, *PNKD*, *CPQ*, *LRP2*, *CHD3*, *SLC9A3R1*, *SETD2* and *CRTC1*. *MET* mutations occurred in 15% of the pRCC samples, with the majority affecting the kinase domain of *MET*. Mapping these changes onto the crystal structure of *MET* kinase suggested they are activating. Other *MET* alterations in pRCC included amplification and overexpression. Six genes were found to be significantly mutated in chRCC (*TP53*, *PTEN*, *FAAH2*, *PDHB*, *PDXDC1* and *ZNF765*) and *TP53* mutations were particularly enriched in the classic form of chRCC. *ERCC2* and *C2CD4C* were both significantly mutated in renal oncocytoma samples. However, low mutation rates in this subtype mean that further investigation is required to ascertain the role of these mutations.

Analysis of copy number changes using single nucleotide polymorphism arrays revealed that pRCC samples frequently showed complete amplification of chromosomes 3, 7, 12, 16, 17 and 20. In contrast the classic chRCC subtype had frequent loss of chromosomes 1, 2, 6, 8, 10, 13, 17 and 21, but the eosinophilic form of chRCC seemed to be diploid. This difference in copy number (along with the observation that *TP53* mutations only occur in the classic chRCC subtype) could assist in distinguishing between these types of chRCC. The most common alteration in renal oncocytomas was the deletion of chromosome 1, but copy number changes were infrequent in this form of tumour.

RNA-seq analysis proved useful in diagnosing the rare tRCC subtype, and tRCC tumours that had *MitF* amplification or gene fusion showed elevated *BIRC7* expression, which might further aid diagnosis and could also be a therapeutic target for this type of nccRCC.

The results of this research have implications for the diagnosis and treatment of nccRCC. The five-gene set could enable accurate disease identification in the clinic and, in turn, assist in treatment decisions. No current therapies have demonstrated efficacy against nccRCC, but this study has discovered new potential therapeutic targets for investigation.

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Original article Durinck, S. *et al.* Spectrum of diverse genomic alterations define non-clear cell renal carcinoma subtypes. *Nat. Genet.* doi:10.1038/ng.3146