Nature Reviews Nephrology | Published online 11 Sep 2017; doi:10.1038/nrneph.2017.131

KIDNEY CANCER

Targeting Wilms tumour

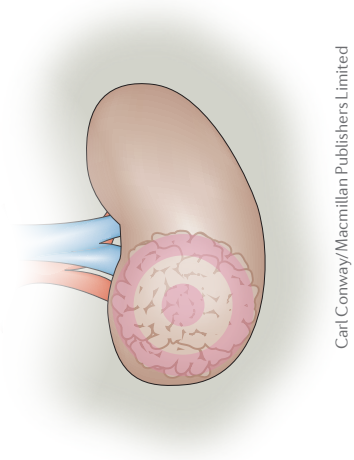
> Many of the genes mutated are involved in two different pathways that are active early in renal development

Wilms tumour, a malignant tumour of the kidney that predominantly affects children, has been linked to mutations in the *WT1* gene in only ~20% of tumours. Now, Elizabeth Perlman and her collaborators have carried out whole-genome or whole-exome sequencing and global gene expression and DNA methylation analysis of Wilms tumour samples to identify mutations or alterations in the remaining ~80% of Wilms tumours. "We used the resources of the Children's Oncology Group and the NCI TARGET initiative to perform comprehensive genomic analysis of 117 Wilms tumours and identified all recurrent mutations (those present in at least two tumours)," explains Perlman.

To validate their initial results, the researchers carried out targeted sequencing of the recurrent mutations in 651 Wilms tumours. Interestingly, many of the genes mutated are involved in two different pathways that are active early in renal development — preservation of the progenitor cell state, or differentiation of progenitor cells, termed 'induction'.

The researchers suggest that Wilms tumours arise through activation of signalling pathways that drive progenitor cell proliferation or through abnormalities of induction. For example, predominantly activating mutations were found in *SIX1* and *SIX2,* which encode homeobox proteins that drive progenitor cell proliferation. In addition, both amplification and mutation of *MYCN*, which encodes a MYC family transcription factor that is crucial for renal progenitor cell renewal, were detected. The investigators also found recurrent mutations or alterations in genes encoding microRNA-processing enzymes, resulting in a global reduction in mature microRNAs, including let-7a, a mediator of cell differentiation early in renal development.

Abnormal induction was linked to mutations in *CTNNB1*, which encodes a protein involved in induction mediated by WNT4 and WNT9 signalling. In addition, mutations in genes linked to transcription elongation (for example, *WT1*, *MLLT1* and *BCOR*) occurred in 30–50% of Wilms tumours.



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"Our analysis ties Wilms tumour oncogenesis to early ontogeny, and suggests that targeting these two pathways would be more efficient than separately targeting the >40 genes that are mutated in Wilms tumour," concludes Perlman.

Grant Otto

ORIGINAL ARTICLE Gadd, S. *et al.* A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3940 (2017)