Sporadic human renal tumors display frequent allelic imbalances and novel mutations of the HRPT2 gene.

Abstract:
Inactivation of the HRPT2 gene encoding parafibromin was recently linked to the familial hyperparathyroidism-jaw tumor syndrome. Patients with this syndrome carry an increased risk of parathyroid and renal tumors. To determine the relevance of HRPT2 for sporadic renal tumors, clear cell, papillary and chromophobe renal cell carcinomas as well as oncocytomas and Wilms tumors were analysed for HRPT2 gene alterations. Loss of heterozygosity (LOH) of HRPT2 was found in seven of 56 (12.5%) clear cell, three of 14 (21%) papillary, six of 10 (60%) chromophobe renal cell carcinomas, three of eight (38%) oncocytomas and four of 10 (40%) Wilms tumors. In addition, two novel HRPT2 point mutations, causing K34Q and R292K changes in parafibromin, were detected in one clear cell carcinoma and one Wilms tumor, respectively. These tumors displayed LOH of the remaining wild-type allele, but interestingly no von Hippel-Lindau (VHL) mutation. Functional analysis revealed that the K34Q mutant species of parafibromin is, unlike wild-type protein, defective in suppressing cyclin D1 expression in vivo. Taken together, these results suggest that renal cancer-associated mutations in parafibromin occur in the absence of VHL mutation, which in turn may contribute to constitutively elevated cyclin D1 expression and abnormal cell proliferation.