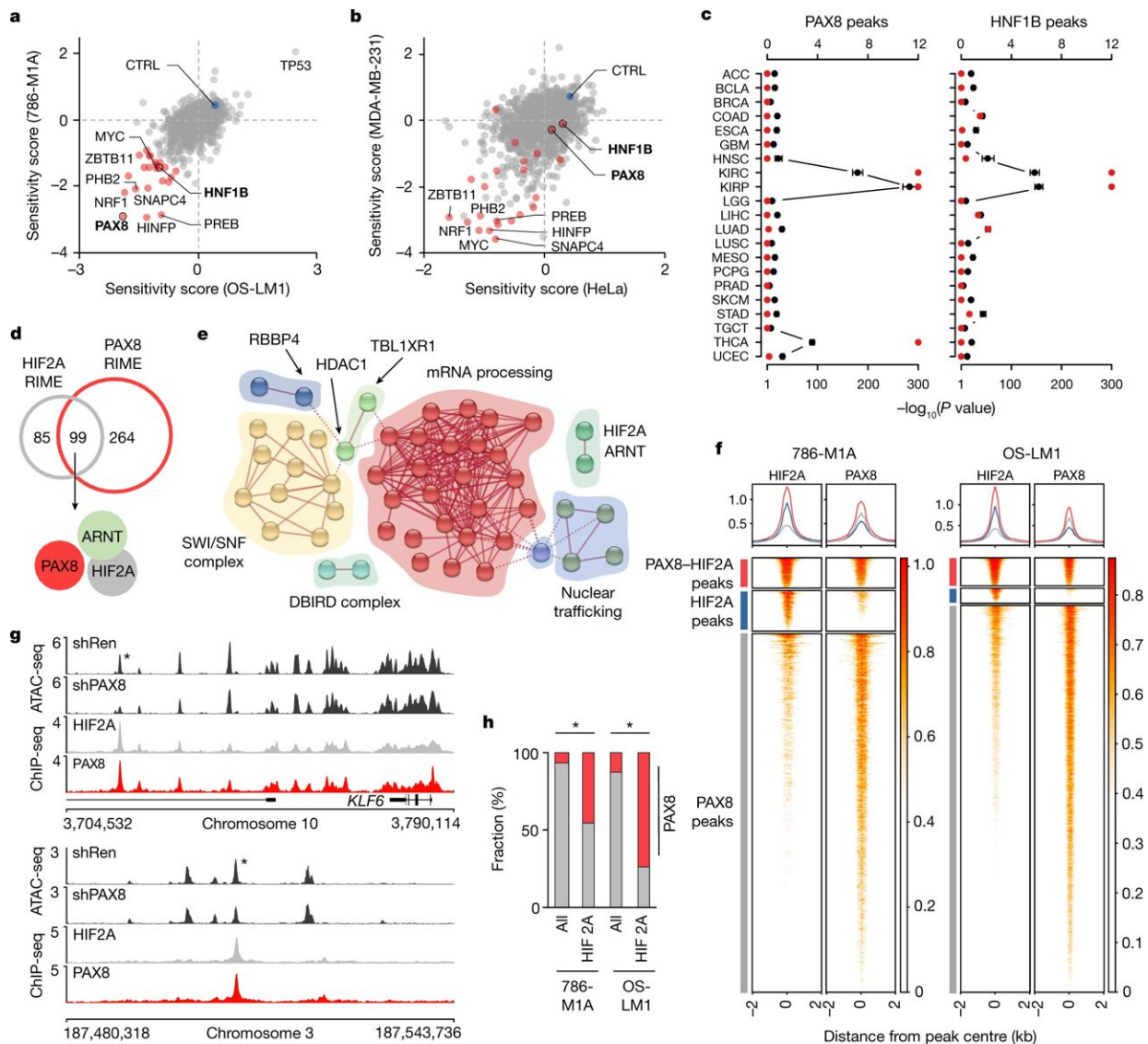


# How common genetic alterations cause kidney cancer

August 9 2022



Chromatin level interaction between the renal lineage factor PAX8 and oncogenic HIF2A in ccRCC. a,b, Pooled CRISPR–Cas9 loss-of-function screen

results of ccRCC cell lines (a) and non-ccRCC cell lines (b). Sensitivity score,  $\log_2$  of the mean of the top three depleted sgRNAs per gene, two replicates per condition, at the end of the assay compared with the start of the assay. ccRCC dependencies are in red. CTRL, average of non-targeting controls. c, Overlap between cancer-type-specific ATAC-seq peaks in TCGA data and those with reduced accessibility after PAX8 and HNF1B depletion in ccRCC cells. Top axis, odds ratio of overlap (black), 95% confidence interval. Bottom axis, P value, one-sided Fisher's exact test (red). d, Overlap between PAX8- and HIF2A-interacting proteins as determined by RIME in 786-M1A cells. e, Network presentation of physical connections between 89 shared nuclear proteins from HIF2A and PAX8 interactomes. Protein names are provided in Extended Data Fig. 4a. f, Heatmaps of HIF2A and PAX8 ChIP-seq signals from 786-M1A and OS-LM1 xenografts (three tumors each) across regions with strong PAX8–HIF2A co-binding (red), predominant HIF2A binding (blue) and predominant PAX8 binding (gray). Top panels show the average signal within each of the three categories in the same colors. g, HIF2A and PAX8 co-bound genomic regions with reduced accessibility following PAX8 depletion. Median ATAC-seq signal from 786-M1A cells expressing a control RNAi construct (shRen, N = 6) or PAX8-targeting RNAi constructs (shPAX8, N = 6). Median HIF2A and PAX8 ChIP-seq signals from 786-M1A and OS-LM1 xenografts, three tumours each. Asterisk indicates a region of interest. h, Fraction of PAX8 peaks (red) in all high-confidence open chromatin regions (all) and HIF2A ChIP-seq peaks in 786-M1A and OS-LM1 xenograft tumors. Asterisk indicates P

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