To date, studies on papillary renal-cell carcinoma (pRCC) have largely focused on coding alterations in traditional drivers, particularly the tyrosine-kinase, Met. However, for a signifi- cant fraction of tumors, researchers have been unable to determine a clear molecular etiol- ogy. To address this, we perform the first whole-genome analysis of pRCC. Elaborating on previous results on MET, we find a germline SNP (rs11762213) in this gene predicting prog- nosis. Surprisingly, we detect no enrichment for small structural variants disrupting MET. Next, we scrutinize noncoding mutations, discovering potentially impactful ones associated with MET. Many of these are in an intron connected to a known, oncogenic alternative-splic- ing event; moreover, we find methylation dysregulation nearby, leading to a cryptic promoter activation. We also notice an elevation of mutations in the long noncoding RNA NEAT1,

and these mutations are associated with increased expression and unfavorable outcome. Finally, to address the origin of pRCC heterogeneity, we carry out whole-genome analyses of mutational processes. In particular, (i) we investigate genome-wide mutational patterns, finding they are governed mostly by methylation-associated C-to-T transitions. (ii) We also observe significantly more mutations in open chromatin and early-replicating regions in tumors with chromatin-modifier alterations. (iii) We reconstruct cancer-evolutionary trees, which have markedly different topologies and suggested evolutionary trajectories for the different subtypes of pRCC