PCPG Pheochromocytoma and Paraganglioma

Subtype	Biology & Expression	Genomic Alterations	Clinical Features
Pseudohypoxia	• Strong HIF-driven signature: upregulation of angiogenesis (VEGF), glycolysis, and hypoxia-responsive genes • CpG-island hypermethylation phenotype	• Krebs-cycle gene mutations (SDHA/B/C/D, SDHAF2, FH) • VHL or EPAS1 mutations	• Often extra-adrenal paragangliomas • Early onset • High metastatic risk, especially with SDHB mutations
Kinase-signaling	• Activation of MAPK/PI3K pathways: elevated RAS/MAPK transcriptional programs • Lower global methylation	• RET, NF1, TMEM127, MAX or HRAS mutations	• Predominantly adrenal pheochromocytomas • Generally benign behavior • Later onset than pseudohypoxia group
Wnt-altered	• Enrichment of WNT pathway targets (AXIN2, LEF1) • Stem-cell and developmental gene signatures	• MAML3 gene fusions (e.g. MAML3–TFG) • CSDE1 mutations	• Rare but aggressive • Intermediate to high metastatic potential • Often larger tumors at presentation