Molecular In My Pocket™

Adult Tumors of the Kidney

Prepared by the Association for Molecular Pathology
Training and Education Committee

Abbreviations

CMA	Chromosomal Microarray Analysis	GUPS	the Genitourinary Pathology Society
CN	Copy Number	LOH	Loss of Heterozygosity

WHO tumor type	Genetic alteration (driver event)	Age of onset (range)	Diagnostic modality	Germline association [red flag markers to trigger germline evaluation]	Comment/secondary alterations	References
MORPHOLOGICALLY DEFINED RCCs (WHO 2022)						
Clear Cell RCC (ccRCC)	3p25 deletion (first-hit at adolescence) + mutation, noncoding/large indels or hypermethylation of *VHL* (3p25.3) (second-hit)	Median 62 years (60-64)	IHC (CA9+, CK7-), CMA (3p loss), NGS (*VHL*, *BAP1*, *PBRM1*, *SETD2*, etc.)	Von Hippel-Lindau (*VHL*), *BAP1* tumor predisposition syndrome	Most cases are sporadic. 3p-deletion often encompasses *VHL*, and *PBRM1*, *SETD2*, and *BAP1* (prognosis).	WHO; 9751329; 29656891; 33210135; 23792563
Papillary RCC	Trisomy 7 and trisomy 17, loss of Y. Low-grade PRCCs: *MET* (7q31.2) alterations	Mostly adult onset	IHC (CK7+, AMACR+, CA9-), CMA (trisomy 7 and trisomy 17, loss of Y), NGS (*MET*, etc.)	Hereditary Papillary RCC (*MET* mutations): if multiple, bilateral and low-grade tumors	WHO 2022 removed subclassification into type 1/type 2 PRCC. High-grade PRCCs: *CDKN2A* aberrations and altered genes from *MYC* and *NRF2/ARE* pathways.	WHO; 26536169; 17409424; 23365135
Chromophobe RCC (chRCC)	Losses of chromosomes 1, 2, 6, 10, 13, 17, 21, Y	Median 59 years (17–92)	IHC (CK7+, KIT+, CA9-), CMA (losses of chromosomes)	Birt–Hogg–Dubé syndrome (bilateral multifocal hybrid morphology - germline *FLCN* mutations (NGS))	May have mutations in *TP53, PTEN, TERT* promoter, *FOXI1, RHCG*, *LINC01187*, and CYCLOPS genes (NGS).	WHO; 11927500; 25155756; 31200327
Oncocytoma of the kidney	Losses of chromosomes 1, 14, 21, X, Y. Many cases have normal copy number profile	Mean 62 years (32–89)	IHC (CK7-, KIT+), CMA (losses of chromosomes)	Rule out Birt–Hogg–Dubé syndrome (bilateral multifocal hybrid morphology - germline *FLCN* mutations (NGS))	Subset show *CCND1* (11q13.3) rearrangements or mutations in mitochondrial genes. Rule out low-grade oncocytic tumor, ChRCC and *SDH*-deficient RCC, etc.	WHO; 26655904; 19386349; 26655904
Mucinous Tubular and Spindle Cell Carcinoma	Losses of multiple chromosomes (1, 4, 6, 8, 9, 13, 14, 15, 22), relative gain of 1q, and *VSTM2A* (7p11.2) overexpression. Mutations in Hippo pathway are common	Median 59 years (13–84)	IHC (CK7+, AMACR+), RNAseq, ISH (VSTM2A overexpression), CMA (losses of chromosomes)	Not known	High-grade tumors: *CDKN2A* or *CDKN2B* deletions and complex genomic aberrations. Differential diagnosis includes papillary RCC.	WHO; 12429795; 27604489; 32879414; 30285995; 27604489; 25395040
Eosinophilic solid and cystic RCC	Biallelic somatic mutations in *TSC1* (9q34.13) or *TSC2* (16p13.3) (mTOR pathway upregulation)	Wide range (14–75)	IHC (CK20 patchy+, cathepsin K+. CK7-, KIT-), NGS (*TSC1/2*)	Tuberous Sclerosis complex associated RCC (germline *TSC1/2*)	Second-hit: *TSC1/2* LOH or second mutations. Same pathway mutations also seen in *TSC2*- or *MTOR*-mutated eosinophilic vacuolated tumor (EVT).	WHO; 29975249; 29668487; 29941307; 28786877; 30303819
RCCs DEFINED BY GENETIC ALTERATIONS (WHO 2022)						
TFE3-rearranged RCC	*TFE3* (Xp11.2) fusions with multiple partner genes, most commonly with *PRCC* (1q23.1), *ASPSCR1* (17q25.3), and *SFPQ* (1p34.3)	Pediatric (40%) and adult onset (~4%)	IHC (TFE3+, Cathepsin K+, AMACR+, CA9-), RNAseq, FISH with break-apart probe (may miss cryptic fusions)	Not known	Several fusions (with *GRIPAP1, RBM10, RBMX,* and *NONO)* are missed by FISH due to cryptic inversions.	WHO; 19228722; 12917640; 33854184
TFEB-altered RCC	*TFEB* (6p21) fusions (with *MALAT1* (11q13.1), *COL21A1, CADM2* (6p12.1), *EWSR1* (22q12.2), *CLTC* (17q23.1), *PPP1R10* (6p21.33), *ACTB* (7p22.1), *NEAT1* (11q13.1), and *KHDRBS2* (6p11.1)) or *TFEB* amplification	Median 31 years (fusions), 65 years (amplification)	IHC (TFEB+, Cathepsin K+, CK20+ in *TFEB*amp, Melanocytic markers+ more in *TFEB*-fusion), FISH break-apart (for fusion or amp), RNA seq (for fusion), CMA (for amplification)	Not known	No clear consensus criteria for *TFEB*-amplified RCC (high vs. low level amplification).	WHO; 24618616; 28840857; 33854184
Fumarate hydratase-deficient RCC	Biallelic germline/somatic *FH* inactivation	Often young adults (20–40s)	IHC (FH lost and/or 2SC diffuse+, CK7-, CD117-), NGS	Hereditary Leiomyomatosis & RCC (HLRCC)	Genetic counselling and germline testing is recommended.	WHO; 26574848; 27635946; 24441663
Succinate dehydrogenase-deficient RCC	Biallelic loss of *SDHB* (1p36.13), *SDHA* (5p15.33), *SDHC* (1q23.3), or rarely *SDHD* (11q23.1) by germline mutation and somatic second-hit (mutation or deletion)	Median 35 years (14–76)	IHC (SDHB lost, CA9-, CK7-, EMA+, AMACR+), NGS, CMA (for large deletions)	Germline variants in one of the *SDH* genes (mostly in *SDHB*, followed by *SDHA* or *SDHC,* and rarely in *SDHD*). Penetrance is low.	Genetic counselling and germline testing is recommended. Mutations in any *SDH* gene leads to SDHB IHC loss. Large deletions might be missed by NGS. Germline *SDHA* variants relatively common with extremely low penetrance.	WHO; 25025441; 25034258; 23060355; 32686200
SMARCB1-deficient renal medullary carcinoma	Biallelic *SMARCB1 (INI1)* inactivation at 22q11.23 (translocation, deletion, LOH)	Variable (childhood to 70s).	IHC (SMARCB1-, EMA+, Vimentin+, OCT3/4+-), FISH (CN, translocation), CMA (CN), NGS if IHC is equivocal (NGS alone not sufficient)	Rhabdoid Tumor Predisposition Syndrome (germline *SMARCB1* mutations) rarely. Young patients of African ancestry with sickle cell trait.	Chromosomal gains/losses reported, most commonly 8q gain. RCCs with secondary loss of *SMARCB1* are classified according to the primary tumor type (i.e. ccRCC with sarcomatoid differentiation).	WHO; 26085875; 29440190; 25299309; 26433572; 30980040; 32359397
ALK-rearranged RCC	*ALK* (2p23.2-p23.1) fusions (with *VCL* (10q22.2), *TPM3* (1q21.3), *EML4* (2p21), *STRN* (2p22.2), and *HOOK1* (1p32.1))	Wide range (3–85 years)	IHC (ALK+, SMARCB1 intact), FISH or RNAseq	Not known	*VCL::ALK* fusions - strong association with sickle cell trait. Rare entity with less than 100 cases reported in adults.	WHO; 21076462; 21213368; 24698962; 28558987; 32467651

RCCs DEFINED BY GENETIC ALTERATIONS (WHO 2022) (con't)						
ELOC (formerly *TCEB1*)-mutated RCC	Biallelic *ELOC* (8q21.11) inactivation (mutations often concurrent with loss of chromosome 8), in the absence of *VHL* alterations and 3p loss	40s-60s	IHC (CK7+, CA9+, GPNMB-), NGS	Von Hippel-Lindau-like disease (no germline *VHL*, but germline *ELOC*) (rare)	Clear cell morphology with papillary architecture. >90% male. GPNMB IHC separates *TSC1/2*/mTOR-altered RCC with fibromyomatous stroma (diffusely positive) from *ELOC*-mutated RCC (negative).	WHO; 25676555; 35323939; 37088333; 31813809
EMERGING OR PROVISIONAL ENTITIES, OTHERS						
Eosinophilic vacuolated tumor	*MTOR* (1p36.22), *TSC2* (16p13.3) or *TSC1* (9q34.13) mutations, resulting in mTOR pathway activation. Losses at 1, 19p, 16p, 7q	Median 50 years (15-72)	IHC (GPNMB+, Cathepsin K+, CD117+, CK7±, CK20-, Vimentin-), NGS, CMA	Tuberous Sclerosis complex associated RCC (germline *TSC1/2*)	One of the few TSC/mTOR-driven RCCs, representing an emerging entity.	33526874; 37627070; 34521993; 30232607
Multilocular cystic renal neoplasm of low malignant potential (MCNLMP)	*VHL* (3p25.3) alterations: ~77% monosomy 3/del(3p), ~25-40% mut	Median 55 years (18-84)	IHC profile similar to CCRCC	Von Hippel-Lindau syndrome	Some cases (5-13%) are diagnosed concurrently with CCRCC.	WHO; 22763870; 27108004; 25381150; 21151099; 29770853
Low-grade oncocytic tumor	*TSC1* (9q34.13), *TSC2* (16p13.3), *MTOR* (1p36.22), *RHEB* (7q36.1) mutations. Deletions at 1p, 19p, 19q	Median 65 years (36–89)	IHC (CK7+, CD117-, vimentin-), NGS	Consider Tuberous Sclerosis Complex (TSC) if multiple tumors	Currently included in WHO "Other eosinophilic oncocytic tumors of the kidney" with somatic *MTOR* or *TSC1/TSC2* mutations.	37845471; 35273336; 34153307; 32299640; 38460672
FLCN-mutated renal tumor (FMT)	Biallelic inactivation of *FLCN* (17p11.2): germline followed by somatic second-hit (mutation, deletion, or copy-neutral loss of heterozygosity/uniparental disomy)	Median 48 years (31-71)	IHC (GPNMB+, SOX9+, mosaic CK7+ and L1CAM), NGS	Birt-Hogg-Dubé syndrome (if history of lung cysts + pneumothorax) - testing should include detection of promoter region and large deletions	Rare somatic mutations without germline predisposition reported, rule out secondary passenger *FLCN* mutations.	40253282; 37182269; 42166008; 40321032
Papillary renal neoplasm with reverse polarity	*KRAS* codon 12	Mean age at 63 years (36-82)	IHC (GATA3+, CK7+, CD117-), NGS, CMA (lack of trisomy 7/17 and Y loss)	Not known	Lacks *MET* alterations (papillary RCC).	31534204; 31953522
Biphasic hyalinizing psammomatous RCC	*NF2* (22q12.2) inactivation (mutations or promoter methylation); often monosomy 22, *PBRM1* (3p21.1), *CYP2A6* (19q13.2) mutations	Median 59 years (43-88)	IHC (CK7+, Merlin loss, melanocytic markers-)	Not known	*NF2* mutations are not specific for this entity and can be seen in other RCCs.	32217839; 27713405
Thyroid-like follicular RCC	*EWSR1::PATZ1* fusion (reported in a subset)	Median 35 years (19-83)	IHC (CK7+, EMA+, cyclin D1+, TTF-1-, Thyroglobulin-), FISH or RNAseq (preferred)	Not known	Follicular morphology. Rare (60 reported cases). Emerging entity, currently a subtype for papillary RCC.	WHO; 34099871

Hereditary RCC — Criteria for Genetic Risk Evaluation (NCCN, HERED-RCC-1). Refer if ≥1 criterion met.

- **Age** (RCC at ≤46 yr; age alone = low sensitivity)
- **Size/laterality** (bilateral or multifocal RCC)
- **Family history** (≥1 first-/second-degree relative with RCC; close relative with known P/LP cancer-susceptibility variant; or unaffected person with ≥2 same-side 1st/2nd-degree relatives with RCC or a first-degree relative meeting criteria who won't/can't test)
- **Histology** (multifocal papillary; FH-deficient/HLRCC-associated; SDH-deficient; BHD-type—multiple chromophobe, oncocytoma, or oncocytic hybrid; or angiomyolipoma + ≥1 additional TSC criterion)
- **Associated tumors, personal or family hx** (clear cell RCC + VHL-associated tumor—CNS/retinal hemangioblastoma, pancreatic NET, pheochromocytoma, paraganglioma, endolymphatic sac tumor; pheochromocytoma/paraganglioma/GIST; cutaneous and/or uterine leiomyomas; pleural or peritoneal mesothelioma or uveal melanoma [BAP1-TPDS]; or any hx otherwise suggestive of a hereditary RCC syndrome)

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