Evaluation and screening for hereditary renal cell cancers

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Reaume and colleagues present a thoughtful guide to genetic screening for inherited renal cancers, including von Hippel Lindau (VHL), hereditary papillary renal cell carcinoma (HPRC), Birt-Hogg-Dubé (BHD), tuberous sclerosis complex (TSC) and hereditary paraganglioma/pheochromocytoma. Our experience has been similar. For patients with familial clear cell renal cancer, we recommend VHL germline mutation testing for those who have either a family history of VHL or a VHL clinical phenotype (i.e., bilateral renal cysts/tumours, pancreatic neuroendocrine tumours, retinal angiomas, CNS hemangioblastomas, etc.). However, in familial renal clear cell patients without a VHL clinical phenotype, we recommend germline karyotypic analysis (to evaluate for the presence of chromosome 3 translocations) or SDHC germline mutation testing. To date, we have not detected a germline VHL gene mutation in a patient/family with clear cell “kidney only” manifestations.

For patients at risk for hereditary papillary renal carcinoma, we recommend germline MET mutation testing starting at age 21. HPRC is, in general, a late onset disease; however, we have identified an early onset MET mutation in which kidney tumours have been detected in patients as young as 19 years old. While bilateral multifocal type 1 papillary RCC is common, hereditary papillary renal carcinoma is truly rare; less than 30 families are known to exist. Germline MET mutations are rarely identified in patients with bilateral, multifocal type 1 papillary RCC with no family history.

The initial diagnosis of Birt-Hogg-Dubé is most often made by clinical findings. In 90% of our BHD families, an individual was found to have cutaneous fibrofolliculomas, while 84% of patients were found to have pulmonary cysts, and nearly 30% had a history of pneumothorax. Although the BHD-associated kidney cancer pathologic phenotype can be variable (mostly hybrid/oncocytic RCC, chromophobe RCC and clear cell RCC), nearly 60% of tumours are hybrid/oncocytic renal cell carcinoma. We recommend germline FLCN testing, beginning at age 21, in families with patients with cutaneous fibrofolliculomas, familial pulmonary cysts/pneumothorax and/or those found to have a hybrid/oncocytic RCC pathology.

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC), which is a hereditary cancer syndrome in which affected individuals are at risk for developing cutaneous and uterine leiomyomas and a potentially aggressive form of type 2 papillary kidney cancer, are characterized by a germline mutation of the gene for the TCA cycle enzyme, fumarate hydratase (FH). We recommend germline FH mutation testing (starting at 8 years of age) for patients with cutaneous/uterine leiomyomas and/or type II papillary RCC. FH germline mutation testing is important in all patients at risk for HLRCC, as HLRCC-associated kidney cancer has the potential to be an aggressive, lethal form of type II papillary kidney cancer which can spread when the tumours are very small. It is recommended that patients affected with HLRCC undergo annual abdominal MRI imaging, as HLRCC-associated kidney tumours have been detected in patients from 10 to 77 years of age.

Succinate dehydrogenase kidney cancer (SDH-RCC) is another TCA cycle gene hereditary kidney cancer syndrome characterized by germline mutation SDHB, SDHC, and SDHD. SDH-RCC families can present with kidney cancers, which often have a characteristic “oncocytic” pathologic phenotype; these families can also develop both kidney cancers and pheochromocytomas/paragangliomas. We recommend SDH germline for patients with familial pheochromocytoma and renal cell carcinoma, as well as those with the characteristic SDHB-deficient pathologic pattern.

We also recommend germline mutation testing in early onset (under age 46) kidney cancer, patients with bilateral, multifocal disease and those with a family history of kid-
ney cancer. We use clinical phenotypic manifestations (as described in Reaume and colleagues), as well as age and kidney cancer pathology as a guide to select which genes to test. For patients with familial clear cell, we consider recommending testing for VHL, SDHC, BAP1, TCS1 and TSC2. For patients with familial type 1 papillary RCC, we generally recommend germline MET testing. For patients with familial type 2 papillary RCC, we recommend germline FH testing. For familial chromophobe RCC, we recommend FLCN, TSC1, TSC2, and sometimes PTEN (depending on the clinical manifestations). For early onset familial RCC, we often recommend SDH and FH germline mutations testing.

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References

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