Last Updated March 2020

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC): *FH* Mutations

HLRCC Risks

- **Cutaneous Leiomyomata**: The majority (76%) of individuals with HLRCC present with a single or multiple cutaneous leiomyomata. Clinically, cutaneous leiomyomata appear as skin-colored to light brown papules or nodules. They occur at a mean age of 25 years (range: age 10-47 years) and tend to increase in size and number with age. Affected individuals note that the skin lesions are sensitive to light touch and/or cold temperature and, less commonly, are painful.[1]
- **Uterine Fibroids:** Uterine leiomyomata, or uterine fibroids, are present in almost all women with HLRCC and they tend to be more numerous and earlier in onset than uterine fibroids in the general population. Most women experience irregular or heavy menstruation and pelvic pain. Women with HLRCC and uterine fibroids may undergo hysterectomy or myomectomy for symptomatic uterine fibroids at a younger age (<30 years) than the general population (45 years).[1-4]
- **Renal Cancer:** The estimated lifetime risk for renal cancer in *FH* mutation carriers is 15%.[5] Most tumors are classified as type 2 papillary renal cancer, which display distinct papillary architecture and characteristic histopathology. However, other types of renal tumors have been reported in individuals with HLRCC including tubulo-papillary renal cell carcinomas and collecting-duct renal cell carcinomas.[6] The median age at detection of renal tumors in individuals with HLRCC is 44 years. Renal cancers associated with HLRCC are more aggressive than those in other hereditary renal cancer syndromes.[3]
- **Pheochromocytoma/Paraganglioma (PCC/PGL):** It has recently been suggested that *FH* mutations may rarely be associated with PCC or PGL and pediatric PCC. [7,8] To date, the observed incidence of *FH* mutations in PCC/PGL cases is approximately 1%. The age range to develop a PCC or PGL in individuals with *FH* mutations is 6-70 years and the extent of disease may vary. The exact risks for PCC/PGL with *FH* mutations remains unclear.

HLRCC Management Recommendations

There is currently no consensus on clinical surveillance for HLRCC. However, several groups have proposed surveillance guidelines. [5,9,10]

	Surveillance Recommendation[1,9,10,11]	**Age of Initiation**	**Frequency**
Full Skin Examination	• Full body skin examination to assess the extent of disease and to evaluate for changes suggestive of leiomyosarcoma • Referral to dermatology as needed for any abnormal skin findings	At time of diagnosis	Annually
Gynecological Exam	• Gynecologic consultation to assess severity of uterine fibroids and to evaluate for changes suggestive of leiomyosarcoma • Ultrasound as needed • Consider myomectomy or hysterectomy for symptomatic fibroids	20 years (or earlier if symptoms)	Annually

Renal Cancer Screening	• Abdominal MRI with renal protocol • May be offered a baseline CT scan and/or ultrasound • Caution: Ultrasound examination alone is never sufficient for the common tumors seen in this syndrome	8 years	Annual MRI
PCC/PGL	• Consider biochemical screening (blood/urine) and imaging studies (CT, MRI)	Clinician Discretion	Clinician Discretion

Natural management

- Estrogen has been shown to stimulate the rapid growth of uterine fibroids. Consider avoiding high-estrogen-content birth-control pills, maintaining a proper body weight (fat cells carry estrogen), eating a low-fat diet to decrease estrogen production, exercising aerobically four to five times a week to regulate hormone production, and avoiding large quantities of foods that are high in phytoestrogens, like yams and soy beans.
- Risk factors for kidney cancer include smoking, obesity, sedentary or inactive lifestyle, and occupational exposures to certain chemicals.

Treatment

- Consider surgical excision, cryoablation, and/or laser excision to remove painful cutaneous leiomyomas; pain medication includes calcium channel blockers, alpha blockers, nitroglycerin, antidepressants, or antiepileptic drugs. [1,12]
- Treatment of uterine fibroids can include gonadotropin-releasing hormone agonists, antihormonal medications, pain relievers, myomectomy, and hysterectomy. [1]
- Total nephrectomy should be considered in individuals with kidney tumors. [1]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *FH* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Rarely, individuals inherit two *FH m*utations (one from each parent) and have fumarate hydratase deficiency.[1]
    - Fumarate hydratase deficiency is characterized by rapidly progressive neurologic impairment including hypotonia, seizures, and cerebral atrophy.
    - *FH* genetic testing for the partner of an individual with a *FH* mutation may be appropriate to clarify the risk of having children with fumarate hydratase deficiency.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

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