FH Pathogenic Variant Carriers: Management Guidelines for Healthcare Professionals

General information

- Germline pathogenic variants (GPV- including class 4 likely pathogenic and class 5 pathogenic variants) in the *FH* gene are associated with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) (OMIM #136850) (also referred to as *FH* Tumour Predisposition Syndrome) and follow an autosomal dominant inheritance pattern.
- *FH* heterozygotes (carriers) are at increased risk of renal cancer, cutaneous leiomyomata and early onset multiple uterine leiomyomas (fibroids).
- There is a strong association with Type 2 papillary renal cancer, but other histological subtypes can occur. HLRCC-associated RCC is now listed as a separate entity in classification of renal neoplasia.
- Uterine fibroids have a characteristic appearance with the presence of orangeophilic, prominent nucleoli that are surrounded by a perinuclear halo.
- Cutaneous leiomyosarcoma and uterine leiomyosarcoma have been reported in some *FH* families, but a clear increased risk is not currently established.
- Phaeochromocytoma and paraganglioma have also been associated with pathogenic variants in *FH.*

Associated risks

Renal cancer	Lifetime risk ≈15-20% with 2-4% incidence below 20 years, mean age ≈early 40s
Cutaneous leiomyomata	Lifetime risk ≈45-80%, mean age of onset ≈30s
Uterine leiomyomata (fibroids)	Lifetime risk ≈40-60%, mean age of onset ≈30s

Management recommendations

Surveillance	-Annual renal MRI from age 10-75 years (To include 3mm slices with immediate evaluation if abnormality is detected due to aggressive nature of disease). -Refer to local Clinical genetics for recommendations on organisation of renal cancer surveillance.
	-Consider annual gynaecology review and USS from age 20 years for females. Management of multiple uterine fibroids should be directed by Gynaecology and may include medical and surgical management.
	-Routine surveillance for phaeochromocytoma and paraganglioma is not currently advised, but patients should be advised on symptom awareness with low threshold for investigation.
Skin management	-Consider referral to Dermatology if cutaneous leiomyomata are present. Treatment for cosmetic reasons and symptomatic lesions may be offered. Surgical excision may be considered for a solitary painful lesion. Multiple lesions may be amenable to treatment by cryoablation and/or lasers. Several medications, including calcium channel blockers, alpha blockers, nitroglycerin, antidepressants, and antiepileptic drugs, have been reported to reduce leiomyoma-related pain.
Lifestyle advice	-Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer.
Family matters	-Refer to clinical genetics for discussion of predictive genetic testing in at-risk family members. -Predictive testing is normally considered from around the age at which surveillance starts. -Refer to clinical genetics for discussions on reproductive options. -Autosomal recessive inheritance of *FH* leads to a metabolic disorder and fumarase deficiency (OMIM #606812).The potential for recessive inheritance in families should be considered

Key references

https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/

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Patient resources

-HLRCC Family Alliance: https://hlrccinfo.org/

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