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 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lifetime risk</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cancer</td>
<td>15-20%</td>
<td>early 40s</td>
</tr>
<tr>
<td>Cutaneous leiomyomata</td>
<td>45-80%</td>
<td>30s</td>
</tr>
<tr>
<td>Uterine leiomyomata (fibroids)</td>
<td>40-60%</td>
<td>30s</td>
</tr>
</tbody>
</table>

### 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 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


### Patient resources

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