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FH Tumor Predisposition Syndrome

Synonyms: Hereditary Leiomyomatosis and Renal Cell Cancer, HLRCC, Multiple Cutaneous and Uterine Leiomyomatosis (MCL/MCUL), Reed's Syndrome

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Summary

Clinical characteristics

FH tumor predisposition syndrome is characterized by cutaneous leiomyomata, uterine leiomyomata (fibroids), and/or renal tumors. Pheochromocytoma and paraganglioma have also been described in a small number of families. Cutaneous leiomyomata appear as skin-colored to light brown papules or nodules distributed over the trunk and extremities, and occasionally on the face, and appear at a mean age of 30 years, increasing in size and number with age. Uterine leiomyomata tend to be numerous and large; age at diagnosis ranges from 18 to 53 years, with most women experiencing irregular or heavy menstruation and pelvic pain. Renal tumors are usually unilateral, solitary, and aggressive. They are associated with poor survival due to clinical aggressiveness and propensity to metastasize despite small primary tumor size. The median age of detection is approximately age 40 years.

Diagnosis/testing

Diagnosis of *FH* tumor predisposition syndrome is established by identification of a heterozygous pathogenic variant in *FH*.

Management

Treatment of manifestations: Surgical excision, carbon dioxide laser, cryotherapy, or electrodessication to remove painful cutaneous leiomyomas. Medications are used as an adjunct for pain relief, and may include drugs that lead to vasodilation (e.g., nitroglycerin, nifedipine, phenoxybenzamine, doxazosin) and/or drugs for neuropathic pain (e.g., gabapentin, pregabalin, duloxetine). Treatment of uterine fibroids can include gonadotropin-releasing hormone agonists, antihormonal medications, intrauterine devices releasing progesterone, myomectomy, and hysterectomy. Consultation with a urologic oncology surgeon familiar with this syndrome should be sought for kidney tumors. Total or partial nephrectomy with wide margins may be carefully considered in some settings.

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Surveillance: Full skin examination every one to two years to assess for extent of disease and evaluate for changes; annual gynecologic consultation to assess severity of uterine fibroids from age 20 years; annual MRI with 1- to 3-mm slices through kidney from age eight years.

Evaluation of relatives at risk: When the *FH* pathogenic variant in the family is known, molecular genetic testing of asymptomatic at-risk relatives provides diagnostic certainty, allowing for early surveillance and treatment.

Genetic counseling

FH tumor predisposition syndrome is inherited in an autosomal dominant manner. If a parent of a proband has an *FH* pathogenic variant, the sibs of the proband have a 50% chance of inheriting the pathogenic variant. Each child of an individual with *FH* tumor predisposition syndrome has a 50% chance of inheriting the pathogenic variant. The degree of clinical severity is not predictable. Preimplantation genetic testing and prenatal testing are possible if the pathogenic variant in the family is known.

Diagnosis

Suggestive Findings

FH tumor predisposition syndrome **should be suspected** in individuals with the following features.

Cutaneous leiomyomata (~50%) [Smit et al 2011, Muller et al 2017, Bhola et al 2018]

- Skin-colored to light brown/reddish papules or nodules distributed over the trunk, extremities, and occasionally on the face and neck
- May be single, grouped/clustered, segmental, or disseminated
- Histopathology shows bundles of smooth muscle fibers with central, long blunt-edged nuclei [Toro et al 2003].

Uterine leiomyomata (uterine fibroids) (~90% of females) [Wei et al 2006, Smit et al 2011, Muller et al 2017]

- Fibroids tend to be numerous and large.
- Fibroids often demonstrate loss of FH staining and positive cytoplasmic staining for S-(2-succino) cysteine [Martínek et al 2015, Andrici et al 2018, Muller et al 2018].

Renal tumors (~15%) [Muller et al 2017]. Usually solitary, highly aggressive renal cell carcinoma (RCC) that metastasizes early

The spectrum of renal tumors includes type 2 papillary, undefined papillary, unclassified, tubulocystic, and collecting-duct carcinoma [Wei et al 2006].

Establishing the Diagnosis

The diagnosis of *FH* tumor predisposition syndrome is established in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *FH* on molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches include **gene-targeted testing** (multigene panel, single-gene testing) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *FH* tumor predisposition syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *FH* tumor predisposition syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *FH* tumor predisposition syndrome, molecular genetic testing approaches can include use of a **multigene panel** or **single-gene testing**:

- A multigene panel that includes FH and other genes of interest (see Differential Diagnosis) may be used as an initial test as it is often the most comprehensive and cost-effective approach. This strategy may yield variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Almost all multigene panels include genes not associated with the condition discussed in this GeneReview. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For FH tumor predisposition syndrome, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Single-gene testing.** Perform sequence analysis and gene-targeted deletion/duplication analysis of *FH* to detect small intragenic deletions/insertions, missense, nonsense, splice site variants, and intragenic deletions and duplications.

Option 2

When the diagnosis of *FH* tumor predisposition syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *FH*) that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *FH* Tumor Predisposition Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FH	Sequence analysis [3]	~90% [4]
	Gene-targeted deletion/duplication analysis [5]	~10% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Toro et al [2003], Alam et al [2005], Wei et al [2006], Gardie et al [2011], Smit et al [2011]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (as described in Human Gene Mutation Database [Stenson et al 2020]) may not be detected by these methods.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

To date, more than 300 families with characteristic features of *FH* tumor predisposition syndrome and a pathogenic variant in *FH* have been reported [Smit et al 2011, Muller et al 2017]. More recent studies have shown wider phenotypic variability in individuals with *FH* tumor predisposition syndrome than previously described in HLRCC.

Clinical Description

FH tumor predisposition syndrome is characterized by cutaneous leiomyomas, uterine leiomyomata (fibroids), and/or renal tumors. Pheochromocytoma and paraganglioma have also been described in a small number of families. Affected individuals may have a single, multiple, or no cutaneous leiomyomas, typically one or more uterine fibroids, and/or a single or no renal tumors. Rarely, individuals may develop multifocal renal tumors. Disease severity shows significant intra- and interfamilial variation [Wei et al 2006].

Cutaneous leiomyomas. Clinically, cutaneous leiomyomas present as firm skin-colored to light brown-colored papules and nodules. These cutaneous lesions occur at a mean age of 30 years (range: age 10-77 years) [Muller et al 2017] and tend to increase in size and number with age. Affected individuals often note that the skin lesions are painful or sensitive to light touch and/or cold temperature [Lehtonen 2011].

Histologically, proliferation of bundles of smooth muscle fibers with central blunt-edged nuclei is observed [Toro et al 2003].

Cutaneous leiomyosarcoma. In a series of 182 individuals with *FH* tumor predisposition syndrome from 114 families, three individuals developed skin leiomyosarcoma [Muller et al 2017]. Due to changes in diagnostic criteria and nomenclature, lesions previously called leiomyosarcoma may have been atypical smooth-muscle neoplasms/leiomyomas [Kraft & Fletcher 2011].

Uterine leiomyomas (uterine fibroids). Women with *FH* tumor predisposition syndrome have more uterine fibroids and onset at a younger age than women in the general population. The age at identification of fibroids ranges from 18 to 53 years (mean: age ~30 years) [Lehtonen 2011]. Uterine fibroids in women with *FH* tumor predisposition syndrome are usually large and numerous and associated with irregular menses, menorrhagia, or pain [Lehtonen 2011]. Women with *FH* tumor predisposition syndrome often undergo hysterectomy or myomectomy for symptomatic uterine fibroids at a younger age. In one series, 59 of 114 women (52%) with *FH*

tumor predisposition syndrome had myomectomy or hysterectomy with median age of 35 (range 25-58) [Muller et al 2017].

Among a cohort of 2,060 women with uterine smooth muscle tumors, a prospective screening program identified a tumor with FH-deficient morphology in 30 individuals (1.4%). Histologic criteria for FH-deficient morphology included alveolar pattern edema and staghorn-shaped blood vessels under low magnification, and smooth muscle cells with a macro-nucleolus surrounded by a halo and eosinophilic globules seen under high magnification [Rabban et al 2019]. Ten women with a tumor with this morphology elected to proceed with germline *FH* molecular testing; of these, five were found to have a germline *FH* pathogenic variant, suggesting that uterine tumor histology could be used to identify individuals with *FH* tumor predisposition syndrome [Rabban et al 2019].

Uterine leiomyosarcoma. Six women with a germline *FH* pathogenic variant and uterine leiomyosarcoma have been reported in the Finnish population; including three individuals with an additional pathogenic variant identified in tumor tissue, and one individual with isolated leiomyosarcoma, decreased FH activity, but no pathogenic variant identified on tumor tissue testing [Lehtonen et al 2006, Ylisaukko-oja et al 2006b]. However, uterine leiomyosarcoma has not been reported in other cohorts [Muller et al 2017]. Due to changes in diagnostic criteria and nomenclature, lesions previously called leiomyosarcoma may in fact be atypical smooth-muscle neoplasms/leiomyomas [Muller et al 2017].

Renal cancer. Most renal tumors are unilateral and solitary; in a few individuals, they are multifocal. The symptoms of renal cancer may include hematuria, lower back pain, and a palpable mass. However, a large number of individuals with renal cancer are asymptomatic. Furthermore, not all individuals with *FH* tumor predisposition syndrome present with or develop renal cancer.

Of 182 individuals with *FH* tumor predisposition syndrome from 114 families, 34 (19%) were diagnosed with RCC(s). The median age at diagnosis was 40 years. Of 31 individuals with follow-up data available, 82% developed metastatic disease: 16 (47%) presented with metastatic RCC (*de novo* metastatic disease) and another 12 (35%) became metastatic within three years. Among individuals with metastatic RCC, median survival was 18 months [Muller et al 2017].

FH tumor predisposition syndrome is associated with a spectrum of renal tumors including type 2 papillary, undefined papillary, unclassified, tubulocystic, and collecting-duct carcinoma [Wei et al 2006].

FH-related RCC often shows loss of FH staining and positive staining for S-(2-succino) cysteine. Immunohistochemistry cannot distinguish between tumors due to *FH* tumor predisposition syndrome and those due to biallelic somatic pathogenic variants.

The Cancer Genome Atlas has additionally reported a CpG island methylator phenotype (CIMP) as the signature *FH*-associated RCC [Cancer Genome Atlas Research Network 2016].

Pheochromocytoma and paraganglioma. In 2014, two studies aimed at identifying new pheochromocytoma and paraganglioma susceptibility genes identified *FH* germline pathogenic variants in seven of 570 affected individuals [Castro-Vega et al 2014, Clark et al 2014]. Subsequently, two individuals with *FH* tumor predisposition syndrome from a French cohort (1%) were diagnosed with pheochromocytoma [Muller et al 2017]. The lifetime risks for pheochromocytoma and paraganglioma are unknown.

Other. In a Finnish population-based study of *FH* tumor predisposition syndrome, four individuals with breast cancer and one individual with bladder cancer were identified. In three of three breast cancers examined, loss of the wild type *FH* allele was noted [Lehtonen et al 2006].

While other tumors have been described in individuals with germline *FH* pathogenic variants, further data will be needed to determine whether these are *FH*-related tumors [Lehtonen et al 2006, Ylisaukko-oja et al 2006a].

Genotype-Phenotype Correlations

No correlation is observed between specific *FH* pathogenic variants and the occurrence of cutaneous lesions, uterine fibroids, or renal cancer [Wei et al 2006].

FH pathogenic variants reported in families with paraganglioma include the following missense and splice site variants: p.Ala117Pro, c.268-2A>G, p.Thr381Ile, p.Ala194Thr, p.Asn329Ser, p.Cys43Tyr, p.Glu53Lys [Castro-Vega et al 2014, Clark et al 2014].

Pathogenic variant c.700A>G; p.Thr234Ala has been identified in approximately ten families with paraganglioma/pheochromocytoma with and without renal cell carcinoma [Author, personal communication].

Penetrance

Penetrance is currently unknown, as most studies have focused on families with clinical manifestations.

Nomenclature

Historically, the predisposition to the development of cutaneous leiomyomas was referred to as multiple cutaneous leiomyomatosis (MCL/MCUL).

Reed et al [1973] described two kindreds in which multiple members exhibited cutaneous leiomyomas and uterine leiomyomas inherited in an autosomal dominant manner. Subsequently, the association of cutaneous and uterine leiomyomas was referred to as Reed's syndrome.

The association of cutaneous and uterine leiomyomas with renal cancer was described in two Finnish families [Launonen et al 2001]. The name hereditary leiomyomatosis and renal cell cancer (HLRCC) was designated.

Germline *FH* pathogenic variants are now known to be associated with a predisposition to a variety of tumors. The term "*FH* tumor predisposition syndrome" acknowledges this emerging understanding.

Prevalence

The prevalence of *FH* pathogenic variants is not known. *FH* tumor predisposition syndrome is likely to be under-recognized.

Genetically Related (Allelic) Disorders

Fumarate hydratase deficiency (fumaric aciduria). Fumarate hydratase deficiency is a rare autosomal recessive metabolic disease resulting from biallelic germline pathogenic variants in *FH*. Fumarate hydratase deficiency is characterized by early-onset severe encephalopathy, seizures, severe developmental delay, and abnormal brain development. Fumaric aciduria is present.

Sporadic tumors with biallelic *FH* variants. Sporadic tumors occurring as single tumors in the absence of any other findings of *FH* tumor predisposition syndrome have been found to have biallelic somatic pathogenic variants in *FH* that were **not** present in the germline.

Differential Diagnosis

Cutaneous lesions. Cutaneous leiomyomas are rare and highly suggestive of *FH* tumor predisposition syndrome. Because leiomyomas are clinically similar to various cutaneous lesions, histologic diagnosis is required.

Uterine fibroids. Uterine leiomyoma is the most common benign pelvic tumor in women in the general population. The majority of uterine fibroids are not associated with an increased risk of other tumors. Characteristic histologic features and loss of expression of FH on immunohistochemistry should prompt germline genetic evaluation [Harrison et al 2016].

Renal tumor. Familial renal cancer syndromes are usually associated with specific renal pathology. Selected familial renal cancer syndromes and their specific renal pathology are summarized in Table 2. All are inherited in an autosomal dominant manner. A study of individuals with aggressive renal cell cancer (RCC) (stage 3 and stage 4) found a high proportion of germline pathogenic variants (16%) [Carlo et al 2018], many of which had not been previously associated with RCC. Known monogenic, syndromic, well-delineated causes of RCC are included in the table below.

Table 2. Familial Renal Cancer Syndrome Comparisons

Disorder	Gene(s)	Renal Tumor	Cutaneous Lesions	Other Common Findings
FH tumor predisposition syndrome	*FH*	Variable; includes: papillary type 2 RCC, undefined papillary, unclassified, tubulocystic, collecting-duct carcinoma	Cutaneous leiomyoma	Uterine fibroids (early onset, multiple lesions)
Von Hippel-Lindau syndrome	*VHL*	Clear cell RCC	None	• CNS hemangioblastoma • Retinal angioma • Renal cysts • Pancreatic cysts • Pancreatic tumors • Pheochromocytoma
Birt-Hogg-Dubé syndrome	*FLCN*	Various: • Oncocytoma (benign) • Chromophobe RCC (malignant) • Hybrid chromophobe/ oncocytic tumor	• Cutaneous fibrofolliculoma • Trichodiscoma • Acrochordon	• Cutaneous fibrofolliculomas • Multiple lung cysts • Spontaneous pneumothorax
Hereditary papillary renal cancer (OMIM 605074)	*MET*	Papillary type 1 RCC	None	None
BAP1 tumor predisposition syndrome	*BAP1*	Clear cell RCC	Atypical cutaneous melanoma (also described as BAPoma, atypical Spitz tumors)	• Mesothelioma (pleural/ peritoneal) • Uveal melanoma • Cutaneous melanoma • Rhabdoid meningioma

CNS = central nervous system; RCC = renal cell carcinoma

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FH* tumor predisposition syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *FH* Tumor Predisposition Syndrome

System/Concern	Evaluation	Comment [1]
Integument	Detailed dermatologic exam	At diagnosis to evaluate extent of disease & presence of atypical lesions
Genitourinary	Gynecology consult	Beginning at age 20 yrs or earlier if symptomatic to assess for severity of fibroids if present
	Baseline thin-slice (1-3mm) renal MRI	• Beginning at age 8 yrs to evaluate for renal tumors • Abdominal CT scan w/contrast may also be performed, although MRI is preferred.
Pheochromocytoma/ Paraganglioma	Baseline blood pressure	• At diagnosis; no uniform guidelines currently exist. • For genotypes assoc w/paraganglioma or persons w/ personal/family history of paraganglioma, consider baseline MRI from skull base through pelvis & fractionated plasma metanephrines.
Other	Consult w/genetic counselor, cancer genetics program, &/or clinical geneticist	

1. For children diagnosed with FH tumor predisposition syndrome, dermatologic exam, baseline blood pressure, and consultation with a genetic counselor or clinical geneticist may occur at diagnosis. MRI is recommended to begin at age eight, and gynecologic exam at age 20 or earlier if symptomatic [Schultz et al 2017].

Treatment of Manifestations

Cutaneous lesions. Cutaneous leiomyomas should be examined by a dermatologist. Treatment of cutaneous leiomyomas may involve the following:

- Surgical excision, especially for a solitary or a few symptomatic lesions, is considered standard therapy [Malik et al 2015, Patel et al 2017].
- Lesions may also be treated by carbon dioxide laser, cryotherapy, or electrodessication [Malik et al 2015, Adams et al 2017, Patel et al 2017].
- Lesions have a high rate of recurrence [Malik et al 2015].
- Medications are used as an adjunct for pain relief, and may include drugs that lead to vasodilation (such as nitroglycerin, nifedipine, phenoxybenzamine or doxazosin) and/or drugs for neuropathic pain (such as gabapentin, pregabalin, and duloxetine) [Patel et al 2017].
- In one small randomized controlled trial, intralesional botulinum toxin improved quality of life [Naik et al 2015].

Uterine fibroids should be evaluated by a gynecologist.

- Most women with *FH* tumor predisposition syndrome require medical and/or surgical intervention earlier than women without an *FH* germline pathogenic variant.
- Medical therapies include gonadotropin-releasing hormone agonists (GnRHa) and intrauterine devices releasing progesterone [Patel et al 2017].
- Surgical options include myomectomy and hysterectomy.
- If surgery is performed, careful histologic examination is recommended to differentiate between atypical smooth muscle neoplasm and leiomyosarcoma.

Renal tumors. Given the aggressiveness and poor prognosis associated with *FH*-related RCC, surgical excision of renal malignancies appears to require earlier and possibly more extensive surgery than other hereditary renal cancers.

- Early detection and surgical excision are critical at the first sign of *FH*-related RCC. Expert opinion should be sought with a urologic oncology surgeon familiar with *FH* tumor predisposition syndrome. Due to metastatic potential, lymph node dissection may be considered for staging even in the setting of small tumors.
- Given the aggressive nature of these tumors, only total nephrectomy was previously recommended. However, partial nephrectomy with a wide margin may be carefully considered in some settings when small, localized tumors may allow for complete excision (see NCI-PDQ® Genetics of Renal Cell Carcinoma).
- Consultation by an expert familiar with this syndrome is indicated.
- Non-surgical approaches such as surveillance, cryoablation, and radiofrequency ablation are not appropriate for the management of *FH*-related renal malignancies [Adams et al 2017].

Surveillance

Regular surveillance with an emphasis on early detection of RCC by clinicians familiar with the clinical manifestations of *FH* tumor predisposition syndrome is recommended. Surveillance may also be considered for individuals with a suspected diagnosis in whom an *FH* pathogenic variant has not been identified, as well as for at-risk family members who have not undergone molecular genetic testing. Surveillance guidelines still require prospective validation, preferably in the context of international multicenter collaboration [Menko et al 2014, Schultz et al 2017].

Table 4. Recommended Surveillance for Individuals with *FH* Tumor Predisposition Syndrome

System/Concern	Evaluation	Frequency
Cutaneous leiomyoma	Full skin exam to assess extent of disease & evaluate for changes	Annually to every 2 yrs from time of diagnosis
Uterine leiomyoma	Gynecologic consult to assess severity of uterine fibroids	Annually from age 20 yrs or at time of 1st gynecologic exam (whichever is earlier), or earlier in symptomatic persons
Renal tumors	• MRI w/contrast w/1- to 3-mm slices through kidney is preferred. [1, 2] • CT w/contrast may be used as an alternative. [3]	Annually starting at age 8 yrs [4]
	Suspicious lesions (indeterminate lesion, questionable or complex cysts) detected at a previous exam should have prompt follow up. [5, 6]	• Early detection is important. • Renal tumors should be evaluated by a urologic oncology surgeon familiar w/*FH* tumor predisposition syndrome.
Pheochromocytoma/ paraganglioma		No uniform guidelines currently exist.

1. Consensus recommendations for surveillance of RCC were developed in the context of an international HLRCC symposium. Renal ultrasound is not recommended for primary surveillance due to low sensitivity to detect small lesions [Menko et al 2014].
2. MRI avoids radiation exposure, though gadolinium-based contrast agents – which are incompletely eliminated from the body – are currently used. However, there are currently no known adverse health effects from gadolinium retention in individuals with normal renal function.
3. NCI-PDQ® Genetics of Renal Cell Carcinoma
4. The recommended age at which to begin renal surveillance has ranged significantly, from as early as age five years [Alrashdi et al 2010] to adulthood [Lehtonen 2011, Smit et al 2011]. Consensus guidelines developed at the HLRCC symposium recommended screening beginning at age eight to ten years [Menko et al 2014]. Consensus pediatric cancer predisposition guidelines developed at an AACR workshop similarly recommend starting at age eight years [Schultz et al 2017].
5. NCI-PDQ® Genetics of Renal Cell Carcinoma
6. Surveillance by an expert in this condition is indicated. In the right clinical scenario, renal ultrasound may be used to further characterize a cystic lesion but should never be used to replace MRI or CT as a primary surveillance modality.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual by molecular genetic testing for the *FH* pathogenic variant in the family in order to identify as early as possible those who would benefit from early surveillance and treatment and reduce costly screening procedures in those who have not inherited the pathogenic variant.

There have been variable recommendations regarding the most appropriate age at which to perform predictive testing for a familial germline FH pathogenic variant. Consensus recommendations from an American Association for Cancer Research (AACR) workshop on cancer predisposition among children and adolescents supports germline testing from age eight years. Surveillance for RCC in heterozygotes is also suggested to begin at age eight years [Schultz et al 2017]. This age was agreed upon as it precedes the youngest reported cases of FH-related RCC. These include an 8.5-cm papillary RCC discovered on first surveillance ultrasound in a child at age 11 years with a palpable renal mass [Alrashdi et al 2010], and an additional child found to have an RCC at age ten years [Menko et al 2014]. Nevertheless, the overall risk of developing RCC before age 20 years remains low (estimated at 1%-2%) [Menko et al 2014].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

_FH_-related RCC

- Many individuals with advanced disease have received vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) or mammalian target of rapamycin (mTOR) inhibitors. Several studies of anti-VEGF and novel tyrosine kinase inhibitor treatment in individuals with *FH* tumor predisposition syndrome and papillary RCC (including papillary type 2 RCC) have been conducted [Linehan & Rouault 2013]. Improvement of progression-free survival in individuals with papillary type 2 RCC with sunitinib was reported [Choueiri et al 2008, Clinical Trials].
- There is also interest in targeting *FH*-related RCC using a metabolic approach such as metformin in combination with vandetanib to inhibit DNA hypermethylation related to fumarate accumulation [Clinical Trials].
- Targeting of tumor vasculature and glucose transport has been attempted using bevacizumab and erlotinib. Park et al [2019] reported long-term response to bevacizumab plus erlotinib after failure of temsirolimus followed by axitinib in an adult with *FH* tumor predisposition syndrome-related RCC [Park et al 2019]. A retrospective analysis of this combination in ten individuals including untreated and previously treated individuals showed an overall response rate of 50% [Choi et al 2019]. A prospective trial of this combination in previously untreated advanced papillary RCC is under way with preliminary results suggesting a 50% (12/20) overall response rate and 100% disease control rate in individuals with *FH* tumor predisposition syndrome [Srinivasan et al 2014].

Fumarate accumulation in FH-deficient cells may lead to a defect in homologous recombination double-strand break repair. This suggests a vulnerability to PARP (poly ADP-ribose polymerase) inhibition demonstrated in cell lines and in mice with *FH*-deficient tumors [Sulkowski et al 2018]. Human clinical trials using combination therapy for these tumors are currently in development [Author, personal communication].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

FH tumor predisposition syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with *FH* tumor predisposition syndrome inherited an *FH* pathogenic variant from a heterozygous parent. A heterozygous parent may or may not have manifestations of *FH* tumor predisposition syndrome.
- Some individuals diagnosed with *FH* tumor predisposition syndrome have the disorder as the result of a *de novo FH* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown because subtle manifestations in parents may not have been recognized and genetic testing data are insufficient.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo FH* pathogenic variant.
- If the germline *FH* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Although no instances of parental germline mosaicism have been reported, it remains a possibility.
- The family history of some individuals diagnosed with *FH* tumor predisposition syndrome may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has confirmed that neither of the parents has the germline *FH* pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of a proband has an *FH* pathogenic variant, each sib of the proband is at a 50% risk of inheriting the pathogenic variant. It is not possible to predict whether symptoms will occur, or if they do, what the age of onset, severity and type of symptoms, or rate of disease progression will be in sibs who inherit a pathogenic variant.
- If the proband has a known *FH* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *FH* tumor predisposition syndrome has a 50% chance of inheriting the *FH* pathogenic variant. The degree of clinical severity in offspring who inherit the *FH* pathogenic variant is not predictable.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has an *FH* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of surveillance, early diagnosis and treatment.

Testing of at-risk asymptomatic family members. Molecular genetic testing of at-risk family members is appropriate to identify the need for clinical surveillance. Those who have a pathogenic variant should be offered regular lifelong surveillance. Family members who have not inherited the pathogenic variant and their subsequent offspring have risks similar to the general population.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Genetic counseling for individuals known to be heterozygous for an *FH* pathogenic variant and reproductive partner testing is recommended. This is particularly important as some *FH* variants may represent hypomorphic alleles and confer risk for fumarate hydratase deficiency in the biallelic state (homozygous or compound heterozygous) even in the absence of manifestations of *FH* tumor predisposition syndrome in the individual or family.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FH* pathogenic variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **HLRCC Family Alliance**
  2001 Beacon Street
  Suite 208
  Boston MA 02135-7787
  Phone: 617-277-5667 ext. 709; 800-767-4845 ext. 709 (toll-free)
  Fax: 858-712-8712; 866-209-0288 (toll-free)
  Email: hlrcc@vhl.org
  www.hlrccinfo.org

- **Kidney Cancer Association**
  Phone: 800-850-9132
  Email: office@kidneycancer.org
  www.kidneycancer.org
- **National Uterine Fibroids Foundation (NUFF)**
  PO Box 9688
  Colorado Springs CO 80932-0688
  Phone: 800-874-7247 (toll-free); 719-633-3454
  Email: info@NUFF.org
  www.nuff.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. FH Tumor Predisposition Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FH	1q43	Fumarate hydratase, mitochondrial	TCA Cycle Gene Mutation Database (FH)	FH	FH

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for FH Tumor Predisposition Syndrome (View All in OMIM)

136850	FUMARATE HYDRATASE; FH
150800	HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER; HLRCC

Molecular Pathogenesis

Introduction. *FH* encodes the enzyme fumarate hydratase (EC 4.2.1.2.). The active form of the enzyme is a homotetramer. It catalyzes the conversion of fumarate to L-malate in the tricarboxylic acid (Krebs) cycle.

Mechanism of disease causation. Germline pathogenic variants in *FH*, plus somatic variants and loss of heterozygosity in tumor tissue, suggest that loss of function of the fumarate hydratase protein is the basis of tumor formation in *FH* tumor predisposition syndrome [Tomlinson et al 2002].

Within FH-deficient RCC, there is impaired oxidative phosphorylation and a shift to aerobic glycolysis, known as the Warburg effect. AMP-activated protein kinase levels are decreased with a variety of downstream effects including decreased p53 levels, lower cellular iron levels and stabilization of hypoxia-inducible factor (HIF)-1α and increased expression of *VEGF* and *GLUT1* [Linehan & Rouault 2013]. These metabolic derangements are the subject of novel efforts to target *FH*-related tumors (see Therapies Under Investigation).

Recent work also suggests that fumarate accumulation in FH-deficient cells leads to defective homologous recombination double-strand break repair, which may provide an additional approach for therapeutic investigation (see Therapies Under Investigation).

***FH*-specific laboratory considerations.** *FH* encodes two protein isoforms, which are targeted to different subcellular locations: the mitochondria and the cytosol. While the reference sequences in Table 5 are for the longer 510-amino acid mitochondrial isoform, protein variant designations may be based on the shorter 467-

amino acid cytosolic. Both designations are found in the literature and in locus-specific databases, as documented by the p.Arg101Pro variant in Table 5. Recently, an alternative transcription initiation mechanism was proposed for the two isoforms [Dik et al 2016], in contrast to previous reports that suggested of alternative translation initiation. For a detailed discussion of the data supporting these mechanisms, see Dik et al [2016].

Table 5. Notable *FH* Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000143.3	c.905-1G>A		Founder variant in Jewish Iranian families [Chuang et al 2005]
NM_000143.3 NP_000134.2	c.1210G>T	p.Glu404Ter	Founder variant reported in Dutch families [Smit et al 2011]
	c.302G>C	p.Arg101Pro (p.Arg58Pro) [1]	Founder variant reported in England & Germany attributed to a Polish ancestor [Chan et al 2005, Heinritz et al 2008]
	c.1431_1433dupAAA (dbSNP: rs367543046)	p.Lys477dup (dbSNP: rs75086406)	In-frame duplication, w/conflicting interpretations of pathogenicity because the assoc w/*FH* tumor predisposition syndrome is unclear [Martínek et al 2015, Zhang et al 2020]
	c.700A>G	p.Thr234Ala	Identified in ~10 families w/ paraganglioma/ pheochromocytoma w/& w/o renal cell carcinoma [2]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions. Designation is based on the FH isoform targeted to the cytosol versus the one targeted to the mitochondrion (see ***FH*-specific laboratory considerations**) [Heinritz et al 2008, Yogev & Pines 2011, Dik et al 2016].
2. Author, personal communication

Chapter Notes

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- 13 August 2020 (jk) Revision: cutaneous lesions (See Differential Diagnosis.)
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- 15 November 2007 (cd) Revision: prenatal diagnosis available on a clinical basis
- 31 July 2006 (me) Review posted live
- 6 March 2006 (jrt) Original submission

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