

# Familial leiomyomatosis

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## Abstract

*Familial leiomyomatosis is defined as the occurrence of multiple cutaneous leiomyomas within several members of a family. Leiomyomas are benign soft-tissue neoplasms that arise from smooth muscle. This rare syndrome is most commonly transmitted by an autosomal dominant trait and may be associated with tumours of other organs. The preferred site of skin lesions seems to be the upper arm, but lower extremities, trunk and face may be affected as well. The individual lesion appears as a pea-sized, dermal, skin-coloured nodule, which may be painful on touch and squeezing. The tumours gradually increase in number over decades. The most common associated features of visceral organs are the development of uterine leiomyomas and renal cell carcinoma. The gene responsible is HLRCC (*hereditary leiomyomas and renal cell cancer*) gene mapped on 1q42.3-43. It encodes for mitochondrial enzyme: fumarate hydratase. Surgical excision or ablation of cutaneous leiomyomas may be helpful. Regular urologic and gynaecologic examinations are recommended.*

## Key words

Cutaneous leiomyomas, visceral tumors, locus 1q42.3-43, *HLRC* gene, fumarate hydratase

## Definition

Familial leiomyomatosis is defined as the occurrence of multiple cutaneous leiomyomas within several members of a family. The tumours are considered to arise from the arrector pili muscles [1]. The syndrome is most commonly transmitted by an autosomal dominant trait and may be associated with tumours of other organs. The condition has first been described about 150 years ago [2].

The syndrome is labelled as [OMIM 150800](#) or – when associated with visceral cancer – as [OMIM 605839](#).

## Synonyms

The condition has been described by various synonyms including “multiple cutaneous and uterine leiomyomas” [1], “familial multiple cutaneous leiomyomas” [3], “cutaneous leiomyomata with uterine leiomyomata” [4], “hereditary leiomyomatosis and renal cell cancer” [5] “dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer” [6] and “familial leiomyomatosis cutis et uteri, or Reed syndrome”.

## Clinical description

### Dermatologic features

The skin lesions usually start during the second decade of life. The preferred site seems to be the upper arm, but lower extremities, trunk and face may be affected as well. The individual lesion appears as a pea-sized, dermal, skin-coloured nodule which may be painful on touch and squeezing [1]. The tumours gradually increase in number over decades. Some lesions tend to become hard and pale on mechanical irritation [3]. The lesions are often inconspicuous and some affected family members may not be aware of the condition before a thorough dermatologic examination establishes the diagnosis. If there are only very few lesions they may be misdiagnosed as scars. Particularly on the trunk, confusion with acne scars may arise, since the first leiomyomas tend to appear at about the same age as acne vulgaris.

Segmental distribution has occasionally been described [1].

### Associated features

The most common associated feature of visceral organs is the development of uterine leiomyomas (uterine fibroids) [5]. While in some families all affected females developed uterine leiomyomas, in others only some females showed uterine lesions. In this syndrome, uterine leiomyomas predominantly occur in the 4<sup>th</sup> decade, but early onset, even in the 2<sup>nd</sup> decade, has been reported.

Rarely uterine leiomyosarcoma has been found, in one case even at the age of 20 years [4,5].

The second visceral tumour, which has been found to be associated with familial cutaneous leiomyomatosis, is renal cell carcinoma. The first report described a case of hypernephroma [4], while consecutive studies specified the renal lesions as papillary renal cell cancer [5]. These lesions only occur in a minority of affected family members. In one series, 6 of 16 carriers developed renal cell carcinoma [5]. It may, however, occur as early as in the 3<sup>rd</sup> decade and may have metastasised at the time of diagnosis.

### Diagnostic methods

The diagnosis of the skin lesions can easily be confirmed by microscopic examination of a skin biopsy. The tumours are characterized by interlacing bundles of smooth muscle cells. Immunohistology reveals positive presence of desmin and smooth-muscle actin [5].

### Frequency

Accurate data is missing, however familial leiomyomatosis is a rare syndrome.

### Etiology

Though a hereditary background with autosomal dominant inheritance and variable expression was assumed already in early clinical descriptions, molecular genetics of the syndrome were only recently described. Linkage analysis mapped the responsible gene to the long arm of chromosome 1 (1q42.3-43 [7]). The responsible gene described later was termed *HLRCC* (hereditary leiomyomas and renal cell cancer) gene [5]. Subsequently, the gene product was identified as fumarate hydratase [6]. The responsible gene is a housekeeping gene encoding a mitochondrial enzyme involved in the tricarboxylic acid cycle and is expressed in all cell types. In affected individuals, enzymatic activity of fumarate hydratase is reduced in peripheral blood cells and virtually absent in tumor cells. Loss of normal chromosome 1q [5] or segmental loss of heterozygosity [1] may play a role in tumorigenesis.

At present it is not yet clear whether different mutations within the fumarate hydratase gene are associated with different probabilities for the development of visceral tumours.

### Management including treatment

Disfiguring or painful cutaneous leiomyomas can be surgically removed, but local recurrences are not uncommon [3]. Laser therapy or electrocoagulation are considered to be ineffective. Tenderness and pain can be ameliorated by nitroglycerin or nifedipin [3], but the degree of subjective discomfort rarely warrants systemic therapeutic intervention.

More important than symptomatic treatment of skin lesions is meticulous follow-up with respect to uterine and renal tumours. Though obviously not all patients affected by familial leiomyomatosis – and probably even not every family – may develop visceral lesions, regular urologic and gynaecologic examinations are recommended.

### Unresolved questions

At present it is not yet clear whether different mutations within the fumarate hydratase gene are associated with different probabilities for the development of visceral tumours.

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