Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis


Heterozygous fumarate hydratase (FH) germline mutations cause hereditary leiomyomatosis and renal cell cancer (HLRCC), an autosomal dominant syndrome characterized by multiple cutaneous piloleiomyomas, uterine leiomyomas and papillary type 2 renal cancer. The main objective of our study was to evaluate clinical and genetic data from families suspected of HLRCC on a nationwide level. All families referred for FH mutation analysis in the Netherlands were assessed. We performed FH sequence analysis and multiplex ligation-dependent probe amplification. Families with similar FH mutations were examined for haplotype sharing. In 14 out of 33 families, we identified 11 different pathogenic FH germline mutations, including 4 novel mutations and 1 whole-gene deletion. Clinical data were available for 35 FH mutation carriers. Cutaneous leiomyomas were present in all FH mutation carriers older than 40 years of age. Eleven out of 21 female FH mutation carriers underwent surgical treatment for symptomatic uterine leiomyomas at an average of 35 years. Two FH mutation carriers had papillary type 2 renal cancer and Wilms’ tumour, respectively. We evaluated the relevance of our findings for clinical practice and have proposed clinical diagnostic criteria, indications for FH mutation analysis and recommendations for management.

Conflict of interest

The authors declare no conflict of interest.
Hereditary leiomyomatosis and renal cell cancer (HLRCC, OMIM #605839) or multiple cutaneous and uterine leiomyomas (MCULs, OMIM #150800) form an autosomal dominant tumour syndrome caused by heterozygous germline mutations in the fumarate hydratase (FH) gene (1, 2). The condition is characterized by multiple cutaneous piloleiomyomas and early-onset, severely symptomatic uterine leiomyomas; in addition, a subset of patients develops renal cell cancer, mainly of the papillary type 2. Patients with both skin and uterine leiomyomas have been described in case reports since the 1950s. The eponym ‘Reed’s syndrome’ is based on the publication by Reed et al. in 1973 (3) on two families with this particular combination of clinical manifestations. In this report, one patient also had disseminated renal cancer. Launonen et al. (1) established the association with papillary type 2 renal cancer. Insight into the molecular genetic background started with the mapping and subsequent identification of the FH gene (1, 2).

The FH gene maps to chromosome 1q42.3-43 and encodes the 50-kDa subunit of the homotrimer FH. Both cytosolic and mitochondrial FH isotypes are known. Whereas the first is possibly involved in amino acid metabolism, mitochondrial FH functions as an enzyme in the tricarboxylic acid (TCA) cycle, where it catalyses the conversion of fumarate into malate (2). In HLRCC, tumour formation presumably follows Knudson’s two-hit model in which tumours arise from the inactivation of the wild-type FH allele in somatic cells (4).

More than 200 families have been reported to carry germline FH mutations. The majority of these families were documented in case series from the United Kingdom, North America and Finland (2, 4–8). Single reports of families from India and Japan suggest that the disorder occurs worldwide (9, 10).

In exceptional cases in which both parents are heterozygous FH germline mutation carriers, homozygous FH germline mutations may occur in the offspring. This leads to fumarase deficiency (OMIM #606812), a severe metabolic disorder characterized by growth retardation and neurological abnormalities. This condition is usually fatal in early childhood (11).

Reportedly, DNA sequence analysis detects mutations in about 90% of families with a clinical picture compatible with HLRCC (5–8). In one family, Ahvenainen et al. (12) found an FH germline deletion using multiplex ligation-dependent probe amplification (MLPA).

Here, we present a systematic nationwide study of FH germline mutation analysis. We examined 33 families with presumed HLRCC by DNA sequence analysis and MLPA testing. We assessed clinical variability in families with identified FH mutations. Based on these data, we propose clinical diagnostic criteria for HLRCC and indications for FH germline mutation analysis. We also consider options for surveillance aimed at early diagnosis and treatment of HLRCC manifestations.

**Patients and methods**

**Family recruitment**

In the Netherlands, FH germline mutation analysis is performed in one single diagnostic laboratory (Radboud University Medical Centre Nijmegen). Patient and pedigree data were collected for all 33 apparently unrelated index patients who have been analysed since FH mutation analysis became available in 2004. These included 29 Dutch probands and 4 from different European countries. Genetic counselling was performed following standard procedures including informed consent. Cutaneous leiomyomas were diagnosed by expert dermatological examination and histological investigation in all cases. Routinely, initial renal imaging was performed after detection of an FH germline mutation. However, long-term surveillance data were not available. Data on five index patients (LMY04, LMY05, LMY10, LMY13, LMY20) have been published previously (13–15).
Nationwide study of HLRCC mutation analysis

Mutation screening

DNA was isolated according to standard techniques. All exons of the FH gene (accession number NM_000143.2) and flanking intron sequences were amplified by polymerase chain reaction (PCR). Primer and PCR amplification data are available upon request (Table S1). Subsequently, sequence analysis was performed using a 3730 automated sequencer (Applied Biosystems, Foster City, CA). Mutation nomenclature follows the guidelines given at http://www.hgvs.org/mutnomen, with the A of the translation initiation codon in the reference sequence numbered as +1. The initiation codon is codon 1. Newly identified missense mutations were analysed using at least 50 healthy controls.

The DNA samples from mutation-negative patients were screened for exon deletions and/or duplications of the FH gene by MLPA analysis with a commercially available kit, according to the manufacturer’s instructions (SALSA P198 kit, MRC-Holland, Amsterdam, the Netherlands; http://www.mrc-holland.com).

Haplotype analysis

Haplotypes were determined by analysis of microsatellite markers surrounding FH (i.e. D1S1634, D1S304, D1S180, D1S1594, D1S2785, and D1S2679) for available family members with a common FH mutation and analysed using the GENEMAPPER program (Applied Biosystems). The genomic localization of the markers was derived from the Marshfield map and the University of California Santa Cruz (UCSC) human genome database (build hg18, October 2006; http://www.genome.ucsc.edu).

Results

Proband data

The indications for FH germline mutation analysis of the 33 families suspected of HLRCC are summarized in Table 1, which also shows the 14 kindreds positive for FH germline mutations. For these 14 families, an FH mutation was confirmed in 35 patients (including the probands). Illustrative pedigrees of three families (LMY05, LMY21, LMY26) are shown in Fig. 1.

Mutation analysis

DNA sequence analysis revealed 10 different germline mutations in 13 families. Of these, 6 were missense mutations (p.Arg233His, p.Gly275Glu, p.His318Tyr, p.Ser334Arg, p.Met382Val, p.Gly397Arg), 3 were non-sense (p.Glu53X, p.Glu404X, p.Met412X) and 1 was frameshift (p.Asn78fsX85).

The mutations p.Arg233His and p.Glu404X were found in two and three different families, respectively. Haplotype analysis revealed identical repeat lengths of several microsatellite markers in the index patients with the recurrent p.Glu404X mutation (Fig. 2), but not in those with the p.Arg233His mutation (data not shown).

MLPA analysis was performed for the index patients from 20 families without a detectable mutation using sequence analysis, which led to the identification of a whole-gene deletion in one index patient (LMY09), denoted as c.1-?_c.*100del.

Clinical findings

Multiple cutaneous leiomyomas occurred in all FH mutation-positive families, whereas no such lesions were present in mutation-negative families (Table 2). In all families with an FH mutation, the cutaneous lesions had been diagnosed...
histopathologically as piloleiomyomas in at least one family member (Fig. 3).

Cutaneous leiomyomas typically became manifest in the second to fourth decade of life. Common locations of involvement were extremities, shoulders and trunk, and to a lesser extent face and neck. The lesions varied from a few to over one hundred and were 0.2–2.0 cm in diameter (Fig. 4). The nodules, erythematous to skin-coloured, were usually distributed in groups. Six patients also

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**Fig. 1.** Pedigrees of three families with a documented pathogenic fumarate hydratase (*FH*) germline mutation. (a) LMY05 (15), the 25-year-old individual III:7 was the only unaffected mutation carrier in our cohort; (b) LMY26; (c) LMY21. Asterisks indicate whether *FH* mutation analysis has been performed for the corresponding individual. LEU, leukaemia; SK, skin cancer; WILMS, Wilms’ tumour.
had scattered lesions. One patient showed only scattered lesions limited to the left upper arm and trunk. During the course of life, lesions had a tendency to grow in size and increase in number. In about 75% of patients the leiomyomas caused symptoms, in particular pain or itching in response to touching or temperature changes. The severity of such symptoms was highly variable.

Uterine leiomyomas occurred in 17 out of 21 female \(FH\) mutation carriers and usually were of early onset (86% < 40 years). The leiomyomas required surgical treatment in 11 out of 17 cases due to severe symptoms of abdominal pain, menorrhagia and metrorrhagia. Treatment consisted of hysterectomy in nine cases and myomectomy combined with oral contraceptives in the
Fig. 3. Characteristic histopathology of a cutaneous piloleiomyoma from patient II:7 from family LMY26 (Fig. 1b). The lesion consists of various bundles of smooth muscle cells interspersed with ample collagen fibres. Characteristic of piloleiomyoma are the elongated and blunt-ended nuclei in the smooth muscle tumour cells (haematoxylin eosin stain, magnification 100×).

Fig. 4. Picture of multiple cutaneous leiomyomas on the upper arm of patient III:11 from family LMY26 (Fig. 1b). The lesions developed when the patient was about 10 years old and subsequently increased in size and number.

Fig. 5. Histopathology of type 2 papillary renal cell carcinoma in patient II:2 of family LMY13. The tumour is composed of voluminous eosinophilic epithelial cells with pseudostratification of large oval nuclei on papillary cores (haematoxylin eosin stain, magnification 100×).

remaining two. The mean age at which surgery was performed was 35 years (range: 25–39 years) (Table 3).

Two unrelated FH mutation-positive families each had a mutation carrier affected by renal cell cancer. One patient had a Wilms' tumour at the age of 2 (III:9 in Fig. 1a). The other individual was initially diagnosed with a clear cell carcinoma of the kidney at the age of 30, but pathological reassessment showed a papillary type 2 renal cell carcinoma (Fig. 5). In a third family, according to family history a patient had died at the age of 21 due to metastatic kidney cancer; no further data were available (Table 3).

In three FH mutation carriers, malignancies other than renal cancer occurred. In each of two families (LMY20, LMY21), one patient had a basal cell carcinoma (Fig. 1c), while patient II:3 in LMY05 had leukaemia (Fig. 1a). Abdominal imaging of proband III:11 from LMY26 (Fig. 1b) revealed an adrenal adenoma. In one family (LMY27), three FH mutation carriers but also a non-carrier had thyroid pathology.

Renal cancers of various histological subtypes were often the indication for FH mutation analysis: 22 individuals in 19 FH mutation-negative families had a history of renal cancer, including 8 clear cell and 4 papillary carcinomas, and 1 renal leiomyosarcoma. The histological subtypes of the remaining cases were unknown. The age at diagnosis, known for 20 patients, was an average of 55 years (range: 37–89).

Discussion

The main objective of our study was the combined analysis and correlation of clinical and genetic data from families suspected of HLRCC on a nationwide level, in order to develop diagnostic criteria and indications for FH mutation analysis. In the Netherlands, diagnostic FH mutation analysis is centralized in one single laboratory and referring human genetics centres throughout the country cooperated closely in the collection of pedigree data. We identified 14 families with a pathogenic FH germline mutation.

A limitation of our study is its retrospective nature in which data were collected from medical records of probands investigated in various clinical genetic centres. Diagnostic procedures and initial renal imaging in probands and family members were documented in detail, but long-term surveillance data were not available.
Table 3. Clinical details of uterine and/or renal pathology in confirmed fumarate hydratase (FH) mutation carriers (*) and clinically affected family members a

<table>
<thead>
<tr>
<th>Family</th>
<th>Patient</th>
<th>Age at diagnosis (years)</th>
<th>Treatment</th>
<th>Age at treatment (years)</th>
<th>Histological subtype</th>
<th>Age at diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMY04</td>
<td>II:4*</td>
<td>39</td>
<td>Hysterectomy</td>
<td>39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY05</td>
<td>II:2*</td>
<td>38</td>
<td>Hysterectomy</td>
<td>38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY06</td>
<td>III:9*</td>
<td>24</td>
<td>Myomectomy</td>
<td>25, 30</td>
<td>Wilms’ tumour</td>
<td>2</td>
</tr>
<tr>
<td>LMY07</td>
<td>III:1*</td>
<td>38</td>
<td>Hysterectomy</td>
<td>38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY09</td>
<td>III:2</td>
<td>35</td>
<td>Hysterectomy</td>
<td>35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY09</td>
<td>LMY09</td>
<td>III:1*</td>
<td>NA</td>
<td>Hysterectomy NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY10</td>
<td>III:2*</td>
<td>22</td>
<td>Hysterectomy</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY13</td>
<td>II:2*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY20</td>
<td>II:1</td>
<td>NA</td>
<td>Hysterectomy</td>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY21</td>
<td>II:14</td>
<td>39</td>
<td>Hysterectomy</td>
<td>39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY23</td>
<td>III:1*</td>
<td>37</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY23</td>
<td>III:4*</td>
<td>NA</td>
<td>Hysterectomy</td>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY25</td>
<td>II:5*</td>
<td>65</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY26</td>
<td>II:7*</td>
<td>27</td>
<td>Hysterectomy</td>
<td>27</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY27</td>
<td>II:4*</td>
<td>30</td>
<td>Hysterectomy</td>
<td>37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY33</td>
<td>III:1*</td>
<td>31</td>
<td>Hysterectomy</td>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY33</td>
<td>III:4</td>
<td>36</td>
<td>Hysterectomy</td>
<td>36</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMY33</td>
<td>III:1*</td>
<td>NA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a All patients listed in this table were females. A minus (−) indicates the absence of pathology or no treatment performed, whereas NA designates that detailed data were not available.

The frequency of HLRCC in the Dutch population is currently unknown. We presume underdiagnosis of the disorder for several reasons: (i) cutaneous leiomyomas may be inconspicuous and asymptomatic; therefore, many affected individuals will not undergo medical examination, (ii) uterine leiomyomas are very common in the general population and a genetic cause is rarely considered, and (iii) papillary renal cell cancer accounts for about 15% of all sporadic malignant kidney tumours and only occurs in a small subset of patients with HLRCC.

Clinical manifestations

In this study, all FH germline mutation carriers older than 40 years had cutaneous leiomyomas. In line with this, Alam et al. (6) observed an 80–100% penetrance of cutaneous lesions in their study group. The clinical expression varied between and within families from a few asymptomatic leiomyomas to hundreds of painful lesions.

Uterine leiomyomas in HLRCC are reportedly of early onset and often cause severe symptoms. Accordingly, more than 80% of female FH mutation carriers in our cohort developed uterine leiomyomas, mainly in early adulthood, two thirds of whom required surgery. We observed renal cancer in 2 out of 35 (6%) FH mutation carriers. Typically, papillary type 2 renal cell carcinoma is associated with HLRCC (16, 17). Collecting duct and clear cell types, as well as oncocytic renal tumours, have also been reported in HLRCC families (5–7, 12, 17, 18). However, Wilms’ tumour has hitherto not been described in this syndrome (15). We are currently investigating a possible causal link between Wilms’ tumour and HLRCC.

We found an adrenal incidentaloma in one FH mutation carrier. In literature, tumours observed in HLRCC include testicular Leydig cell tumours, ovarian cystadenomas, gastrointestinal stromal tumours (GISTs) and adrenal gland tumours (4, 19–22). Our finding may support the proposed causal relationship between HLRCC and adrenal tumours (19).
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Table 4. Fumarate hydratase (FH) germline mutations detected in our case series by DNA sequence analysis

<table>
<thead>
<tr>
<th>FH germline mutation</th>
<th>Amino acid change</th>
<th>Mutation type</th>
<th>Mutation published previously (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1-?c.*100del</td>
<td>p.75</td>
<td>Whole-gene deletion</td>
<td>(2, 6, 18)</td>
</tr>
<tr>
<td>c.157G&gt;T</td>
<td>p.Glu53X</td>
<td>Non-sense</td>
<td>Novel</td>
</tr>
<tr>
<td>c.233del</td>
<td>p.Asn78fsX85</td>
<td>Frameshift</td>
<td>(14)</td>
</tr>
<tr>
<td>c.698G&gt;A</td>
<td>p.Arg233His</td>
<td>Missense</td>
<td>(2, 5, 7, 18, 27)</td>
</tr>
<tr>
<td>c.952C&gt;T</td>
<td>p.His318Tyr</td>
<td>Missense</td>
<td>(5, 34)</td>
</tr>
<tr>
<td>c.1002T&gt;G</td>
<td>p.Ser334Arg</td>
<td>Missense</td>
<td>(14)</td>
</tr>
<tr>
<td>c.1144A&gt;G</td>
<td>p.Met382Val</td>
<td>Missense</td>
<td>Novel</td>
</tr>
<tr>
<td>c.1189G&gt;A</td>
<td>p.Gly397Arg</td>
<td>Missense</td>
<td>(18, 33)</td>
</tr>
<tr>
<td>c.1210G&gt;T</td>
<td>p.Glu404X</td>
<td>Non-sense</td>
<td>(13)</td>
</tr>
<tr>
<td>c.1234del</td>
<td>p.Met412X</td>
<td>Non-sense</td>
<td>Novel</td>
</tr>
</tbody>
</table>

The mutation code in column ‘amino acid change’ is the same notation as used in the online FH mutation database (26). Pathogenicity of missense mutations is indicated by: †, evolutionary conservation of the amino acid; ‡, a known functional domain of FH is affected by the mutation; and §, the absence of the change in control alleles (number added).

Mutation spectrum

The 11 different FH germline mutations detected in this study are presented in Table 4. The two missense mutations p.Gly275Glu and p.Met382Val have not been reported previously. These missense changes are likely to be pathogenic as the respective amino acid changes affect residues of the encoded FH protein which are highly conserved throughout evolution. In addition, we found cosegregation of these mutations with clinical manifestations and the absence of the mutations in at least 100 control alleles. The novel c.157G>T mutation (p.Glu53X) and c.1234del (p.Met412X) mutations were each found in one family and are predicted to be pathogenic, as the premature termination of protein translation leads to either non-sense-mediated decay of the resulting mRNA or production of a truncated FH protein. MLPA of families with a negative DNA sequence analysis revealed a whole-gene deletion in one family. This indicates that MLPA testing is a valuable complement to FH sequence analysis.

Linkage analysis showed that two of the three families (LMY10, LMY20) with the Glu404X mutation are likely to be related. The index patient from the third family had different nucleotide repeat frequencies on the two markers farthest upstream from FH, which could be due to a single recombination event. The Glu404X mutation in the third family (LMY07) thus may represent the same founder mutation. This is in line with the fact that all three families live in the same province in the Netherlands. Founder mutations have previously been shown to underlie HLRCC. For example, Chuang et al. (23) found the 905-1G>A FH mutation in four families of Jewish Iranian origin. Evidence for a founder effect of the c.173G>C FH mutation was observed in a German and English family (24, 25).

All reported variants of FH are documented in an online database (26). Including the four novel mutations detected in our study, 82 different pathogenic FH germline mutations have now been found to underlie HLRCC. Of these, 21 have been detected in families with renal cancer. These are 11 missense, 7 frameshift and 2 non-sense changes as well as 1 splice-site change, and they are equally distributed over the FH gene, excluding exon 6 (Fig. 6). Renal cancer does not always develop in families with one of these mutations. In our cohort for example, the c.Arg233His mutation was observed in two families with and without renal cancer, respectively. In total, this presumed hotspot mutation has now been detected in 24 families, whereas renal cancer occurred in only 7 (2, 5, 7, 18, 27, 28). Based on these data, no indication for a genotype–phenotype correlation was found. It is likely that all FH germline mutations are associated with a varying range of clinical manifestations (18).

Clinical and molecular diagnosis

We did not find FH germline mutations in 19 of 33 kindreds with suspected HLRCC. Notably, evaluation of these families did not reveal strong clinical indications for HLRCC. In particular, no cutaneous leiomyomas were reported. Women from these families with severe clinical symptoms due to uterine leiomyomas required treatment at an average age of 47 years, which is more than 10 years older than the average for affected female FH mutation carriers. Kiuru et al. (29) showed the presence of FH germline mutations in 1–2% of apparently sporadic early-onset uterine leiomyomas. In our cohort, uterine leiomyosarcoma was the indication of FH mutation analysis for three probands, none of whom showed FH germline mutations. Renal cancer was also an important indication for FH mutation analysis. However, neither age at diagnosis nor histological subtype...
was in fact indicative of HLRCC in families without an \( FH \) mutation.

Based on data from previous reports and our study group, we propose criteria for the clinical diagnosis of HLRCC (Table 5). A likely or suspected clinical diagnosis should be confirmed by detection of a pathogenic \( FH \) germline mutation. Indeed, \( FH \) mutation analysis was positive for all our probands with a likely clinical diagnosis of HLRCC according to these criteria, whereas no \( FH \) mutations could be detected in index patients who did not fulfill the clinical diagnostic criteria. The accurateness of our criteria should be further evaluated prospectively.

\( FH \) germline mutations are rare in apparently sporadic renal cell cancer (25). However, \( FH \) mutation analysis might be justified for all patients with type 2 papillary renal cell carcinomas younger than 40 years. The yield of \( FH \) mutation analysis is probably low in families in which multiple members have uterine leiomyomas as sporadic uterine leiomyomas are common in the general population. Due to the rareness of uterine leiomyosarcoma in HLRCC, \( FH \) mutation analysis only seems indicated if more signs indicative of HLRCC are present in the index patient or family. We found no reason for referral of patients with leiomyomas in other organs than skin or uterus, as such

<table>
<thead>
<tr>
<th>Table 5. Proposed criteria for the clinical diagnosis of hereditary leiomyomatosis and renal cell cancer (HLRCC)(^a)</th>
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<tbody>
<tr>
<td><strong>Major criterion</strong></td>
</tr>
<tr>
<td>• Multiple cutaneous piloleiomyomas, histopathologically confirmed.</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>• Surgical treatment for severely symptomatic uterine leiomyomas before age 40.</td>
</tr>
<tr>
<td>• Type 2 papillary renal cell carcinoma before age 40.</td>
</tr>
<tr>
<td>• A first-degree(^b) family member who meets one of the above-mentioned criteria.</td>
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</table>

\( a \)The diagnosis is likely when a proband meets the major criterion. HLRCC may be suspected when a proband meets at least two minor criteria.

\( b \)Occurrence of severely symptomatic uterine leiomyomas <40 years in second-degree paternal family members may also be relevant.

leiomyomas have not yet been reported in association with HLRCC.

Management and surveillance

Cutaneous leiomyomas may cause serious pain and cosmetic distress. Skin lesions were sensitive in 90% of individuals with cutaneous leiomyomas documented by Wei et al. (7) We found symptoms in approximately 75% of \( FH \) mutation carriers affected by cutaneous leiomyomas. Whereas single
painful skin lesions can easily be treated by wide surgical excision, management of multiple symptomatic lesions is difficult. Treatment options include pharmaceutical agents (i.e. nifedipine, gabapentine and doxazosine) and invasive therapy, such as extensive surgical excision, CO2 laser ablation and cryotherapy. However, as treatment outcome is highly variable, additional strategies are needed (30).

Uterine leiomyomas in HLRCC are of early onset and cause severe clinical symptoms. In total, 70% of women with uterine leiomyomas reported by Toro et al. (5) were younger than 30 years old at the time of diagnosis. In our study group, 35 years was the mean age at which surgery was performed. Annual gynaecological ultrasound examination of female FH mutation carriers starting at age 20 may reveal asymptomatic leiomyomas, which could be monitored for future development. In addition, although leiomyosarcoma is probably rare, early signs of malignancy may be detected (i.e. inhomogeneous internal pattern, central necrosis, irregular vessel distribution) (31). Women affected with HLRCC should be counselled about family planning and treatment options.

The main focus of management in HLRCC is prevention of disease and death due to renal cancer. Relevant issues are the lifetime risk of renal cancer in FH mutation carriers, age at onset, biological behaviour of the disease and options for early diagnosis and treatment. However, current knowledge regarding these issues is limited.

Renal cancer risk apparently cannot be attributed to specific genotypes. It has been suggested that the risk could be increased in certain families due to shared genetic and environmental factors. If proven, surveillance for renal cancer might be aimed at only those families in which renal cancer had occurred previously. However, Vahteristo et al. (32) found no evidence for genetic modifiers of renal cancer risk in HLRCC and concluded that all FH mutation carriers may have an increased renal cancer risk.

Previous reports showed that among 66 FH mutation carriers with renal cancer the mean age at diagnosis was 43 (range: 11–90 years). The course of the disease was aggressive and approximately two thirds presented with stage III/IV disease at the time of diagnosis. In contrast to other forms of hereditary renal cancer, both unifocal and unilateral presentations are common (5, 6, 16, 18, 23).

In our study group, we have recommended renal ultrasound and magnetic resonance imaging (MRI) at the age of 20, followed by annual MRI and semi-annual ultrasound examinations. Based on the data of Vahteristo et al. (32), surveillance should be recommended for all FH germline mutation carriers. As renal cancer in all FH germline mutation carriers. As renal cancer in HLRCC has occurred before age 20, it has been proposed that screening should start at the age of 18 or even 5 years (32, 33). Prospective studies should provide data for evaluation of current policies. Due to the aggressive nature of HLRCC renal carcinoma, treatment should probably be prompt and include total nephrectomy. Experience with nephron-sparing surgery is limited (17).

Conclusion

This study generated additional data on the clinical and genetic variability of HLRCC and allowed comparison of FH mutation-positive with mutation-negative families. Genomic deletions can be detected by complementing MLPA testing to DNA sequence analysis. FH mutations were found in all families with cutaneous leiomyomas; these skin lesions seem to be a typical and highly penetrant feature of the syndrome. Uterine leiomyomas often lead to severe symptoms, which warrant counselling about family planning and treatment strategies. Renal cell cancer is infrequent but aggressive and may occur at a very young age. We propose frequent renal imaging with MRI and ultrasound. Multi-centred studies providing long-term follow-up data will lead to further development of HLRCC management.

Supporting Information

The following Supporting information is available for this article: Table S1. PCR conditions. Fastmix: GeneAmp Fast PCR mastermix (Applied Biosystems). 360 MIX: Amplitaq Gold 360 Mastermix (Applied Biosystems).

Additional Supporting information may be found in the online version of this article.

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