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Multiple cutaneous leiomyomas leading to discovery of novel splice mutation in the fumarate hydratase gene associated with HLRCC

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TITLE PAGE

Multiple cutaneous leiomyomas leading to discovery of
novel splice mutation in *Fumarate Hydratase gene*
associated with HLRCC

Short Running Title:
Cutaneous Leiomyomas & HLRCC

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MAIN TEXT

(i) ABSTRACT & KEYWORDS

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is a rare autosomal dominant condition, which manifests as cutaneous leiomyomas (CL), uterine fibroids and renal cell cancer (RCC). We describe the case of a 53-year-old woman who presented with multiple cutaneous leiomyomas with a novel heterozygous canonical splice site mutation in intron 9 of the Fumarate Hydratase (*FH*) gene IVS 9-1 G>C (NM_000143.3:c 1391-1 G>C) that was not detected on initial screening of a mutation hotspot but picked up on sequencing the remaining exons and splice site junctions. This report highlights the importance of clinical suspicion in the diagnosis of HLRCC in the absence of a family or personal history of cancer and despite initial genetic testing being negative.

Keywords: Cutaneous Leiomyomas (CL), Renal Cell Cancer (RCC), Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Fumarate hydratase (FH), splice site mutation

(ii) TEXT

INTRODUCTION

Cutaneous leiomyomas (CL), also known as piloleiomyomas, are benign smooth muscle tumours arising from arrector pili muscle of hair follicles. Isolated leiomyomas are usually sporadic but where there is more than one lesion they most often occur as part of a syndrome known as Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) (OMIM. 150800).¹ HLRCC is a rare autosomal dominant condition with approximately 300 families reported in the medical literature. It manifests as CL, uterine fibroids and a 15% lifetime risk of developing papillary type II RCC.²⁻³ It is caused by germline heterozygous mutations in *FH* located at chromosome 1q42.1. *FH* encodes for the Krebs cycle enzyme responsible for converting fumarate to malate and it is also thought to act as a tumor suppressor gene.^{1-2,4} To date, 150 distinct *FH* germline mutations have been identified, with more

than 50% being missense mutations.⁵ There is no evidence to suggest a genotype-phenotype relationship for *FH* mutations.⁴

We present the case of a 53 year old woman with multiple CL which led to the diagnosis of HLRCC, highlighting the importance of cutaneous manifestations in the diagnosis of this condition.

CASE REPORT

A 53 year old Caucasian woman was investigated because of a clinical suspicion of HLRCC. She had multiple skin papules on her back, bilateral arms and legs (Figure 1A and 1B). She complained of intermittent allodynia provoked by contact of her clothes on these lesions. She also had menorrhagia secondary to uterine fibroids. There was no significant family history of malignancy and in particular no one had been affected by RCC.

On examination, she had multiple small, non-pigmented papules predominantly on her back and upper arms. They ranged from 3-10 mm in diameter and were tender on palpation. She was non-dysmorphic and did not have any neurocutaneous stigmata.

Histology from previous biopsies of these lesions reported proliferation of bundles of smooth muscle fibers consistent with CL. She had a pelvic ultrasound which confirmed the presence of multiple uterine fibroids.

A clinical diagnosis of HLRCC was made and with genetic testing requested for confirmation. Genomic DNA was obtained from the patient's blood leucocytes and was sent to GeneDX Laboratories, an accredited laboratory. Initial testing, known as Tier 1 analysis, involved sequencing a mutation "hotspot" in exon 5 and its flanking splice site regions. The test revealed no mutation and had a quote mutation detection rate of 34%. Our strong clinical suspicion led us to request sequencing the remaining exons and their splice site junctions, so called Tier 2 analysis. This revealed a heterozygous intronic variant, NM_000143.3:c 1391-1 G>C. This variant results in a single base substitution one nucleotide before the 5' end of exon 10 thus disrupting the AG splice acceptor site (Figure 2A and 2B). This canonical splice site variant is predicted to lead to either the loss of exon 10 or absence of the gene product by lack of transcription or nonsense-mediated mRNA decay. Loss of function has been shown to be disease causing.⁶ Furthermore, as *FH* functions as a homo-tetramer, it may also be susceptible to dominant-negative effects in heterozygous mutations as well.¹ The

mutation is novel and specific to the patient's phenotype. According to the ACMG Guidelines, this variant is classified as pathogenic.⁷

The patient was counseled on her risk of developing RCC and referred to a urologist for surveillance. *FH* predictive testing was offered for all her first-degree relatives.

DISCUSSION

The coexistence of skin and uterine features was first recognised by Reed in 1973.⁸ Launonen et al described the association with RCC in 2001.⁹ RCC associated with HLRCC tend to be aggressive and metastasise even if the primary tumour is small. 10-16% of patients with HLRCC are found to have kidney tumours at the time of diagnosis.^{2,5} Toro et al found that two thirds of *FH* mutation carriers who had renal cell cancer died within 5 years with metastatic disease.² There is no evidence for a lower RCC risk in individuals with a negative family history for RCC.⁴ Early detection and management of RCC in people with HLRCC is important in order to maximise the chance of survival. There is debate about optimal screening for HLRCC, however accepted recommendations such as the EviQ guidelines propose annual renal MRIs, annual gynaecology review for symptomatic fibroids and skin examinations for CL.³

The presence of multiple CL should raise the suspicion of HLRCC and are found in the majority of patients who are *FH* mutation positive.^{2,10} In one study, CL was found in all affected patients over the age of 40.¹⁰ Smit et al have proposed clinical and histopathologic criteria based on the clinical features of 35 *FH* mutations carriers. Multiple CL with at least one histologically proven lesion confirms the diagnosis. In patients who do not have CL, at least 2 minor criteria are required for the diagnosis of HLRCC (Table 1).¹⁰

CONCLUSION

HLRCC is a rare disorder associated with a significantly increased risk of RCC. Our case demonstrates the important role of dermatologists in identifying people with the condition. A definitive diagnosis of HLRCC allows for early detection and treatment of RCC and provides testing to identify at risk family members.

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(iv) FIGURE LEGENDS

Figure 1A: Right upper arm

Figure 1B: Close up of cutaneous leiomyomas on right lateral forearm

Figure 2A: Schematic diagram of *FH* with the location of the variant found in our patient marked with a red arrow. This variant is predicted to disrupt the AG splice acceptor site and is predicted to lead to either the loss of exon 10 or absence of the gene product by lack of transcription or nonsense-mediated mRNA decay.

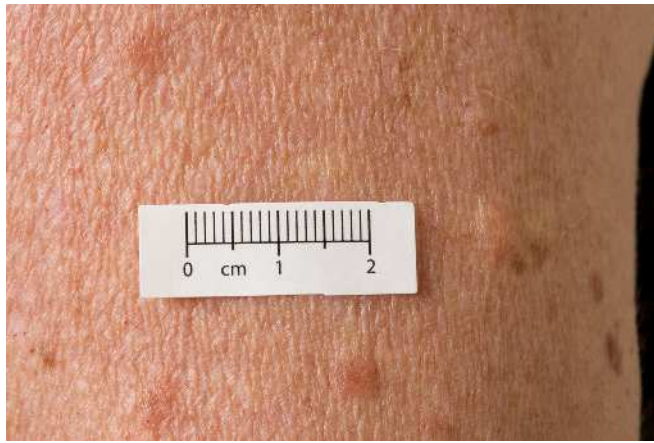
Figure 2B: Chromatogram of the novel heterozygous *FH* mutation with the G > C transversion (indicated by arrow) compared to the normal control. This was performed through direct sequencing of the *FH* gene using DNA extracted from patient's blood sample. (Courtesy of GeneDX Laboratories)

(v) TABLE

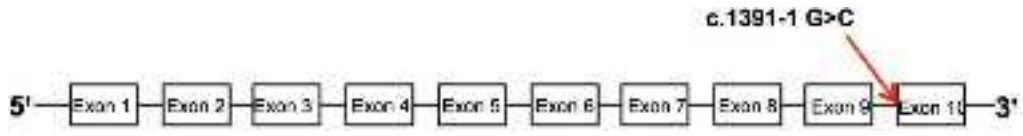
Major Criteria	Minor Criteria
1) Multiple cutaneous leiomyomas, at least one histologically confirmed lesion	1) Solitary cutaneous leiomyomas & family history of HLRCC 2) Type II papillary RCC before 40 years old 3) Surgical treatment of severely symptomatic uterine fibroids before 40 years old 4) First degree relative who meets one of the above-mentioned criteria. The occurrence of severely symptomatic uterine leiomyomas before 40 years old in second-degree paternal family may also be relevant



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