# Case Letter

## An Unusual Case of Sporadic Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome

To the Editor:

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCCS) is a rare, highly penetrant, autosomal-dominant disorder that has been reported in approximately 200 families worldwide.[1,2] More than 90% of patients with HLRCCS develop multiple cutaneous leiomyomata, frequently in a segmental distribution, that increase in number and size with age. The extent of skin lesions is variable, even within the same family. Approximately 90% of female family members also have symptomatic uterine leiomyomata; 10% to 16% of these patients develop aggressive renal cell carcinomas,[3] with more than 50% dying of metastatic disease within 5 years of diagnosis. Clinical diagnosis is established by the presence of multiple cutaneous leiomyomata, at least 1 of which should be histologically confirmed, or by a single leiomyoma in the presence of a positive family history.[4]

Mutations of fumarate hydratase (FH), a Krebs cycle enzyme that interconverts fumarate and malate, have been implicated in this syndrome.[5] The homotetrameric 50 kDa protein exists in the mitochondrial matrix and the cytoplasm. Diagnosis is confirmed by molecular genetic testing for FH mutations or rarely by demonstrating reduced activity of FH enzyme. So far, at least 155 variations in DNA sequence of FH have been identified in HLRCCS. However, no definite genotype-phenotype correlations have been established yet. We present the case of a sporadic form of HLRCCS, which is rare.

A 27-year-old man presented with multiple slowly growing, painful lesions on the chest and back of 11 years' duration. Physical examination revealed approximately twenty 2- to 4-mm pink-tan papules on the left side of the chest and several 2- to 7-mm tan-pink papules on the upper back (Figure 1A). The lesions were tender to touch, pressure, and cold temperatures. Microscopic examination of one of the lesions on the back showed

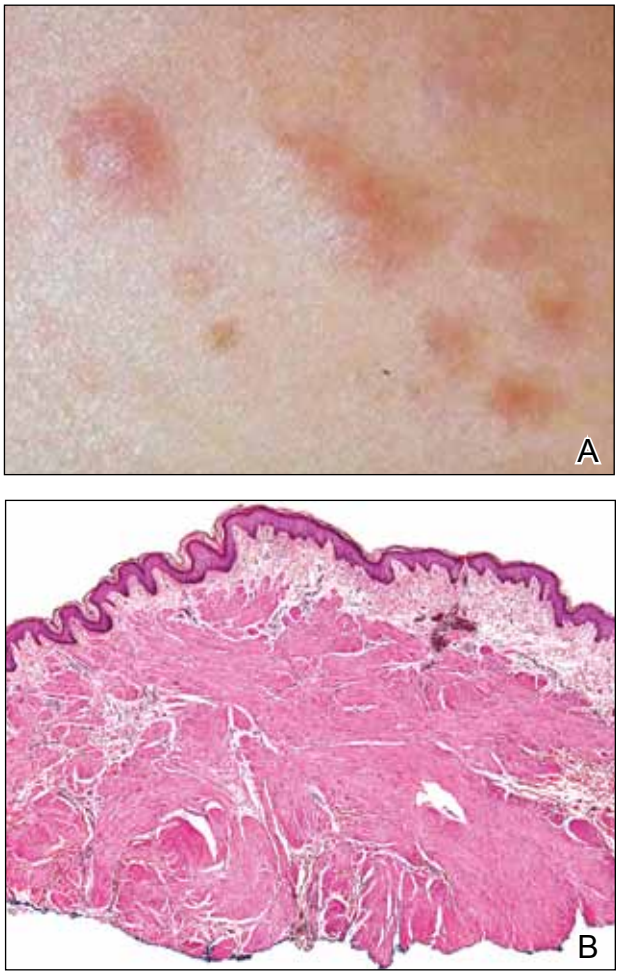


**Figure 1.** Cluster of slow-growing, 2- to 7-mm, slightly erythematous papules on the upper back (A). Shave biopsy showed an unencapsulated dermal proliferation composed of interlacing fascicles of smooth muscle bundles with bland morphology, cigar-shaped nuclei, and lack of mitotic activity, compatible with cutaneous leiomyoma (B)(H&E, original magnification ×40).

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The authors report no conflict of interest.

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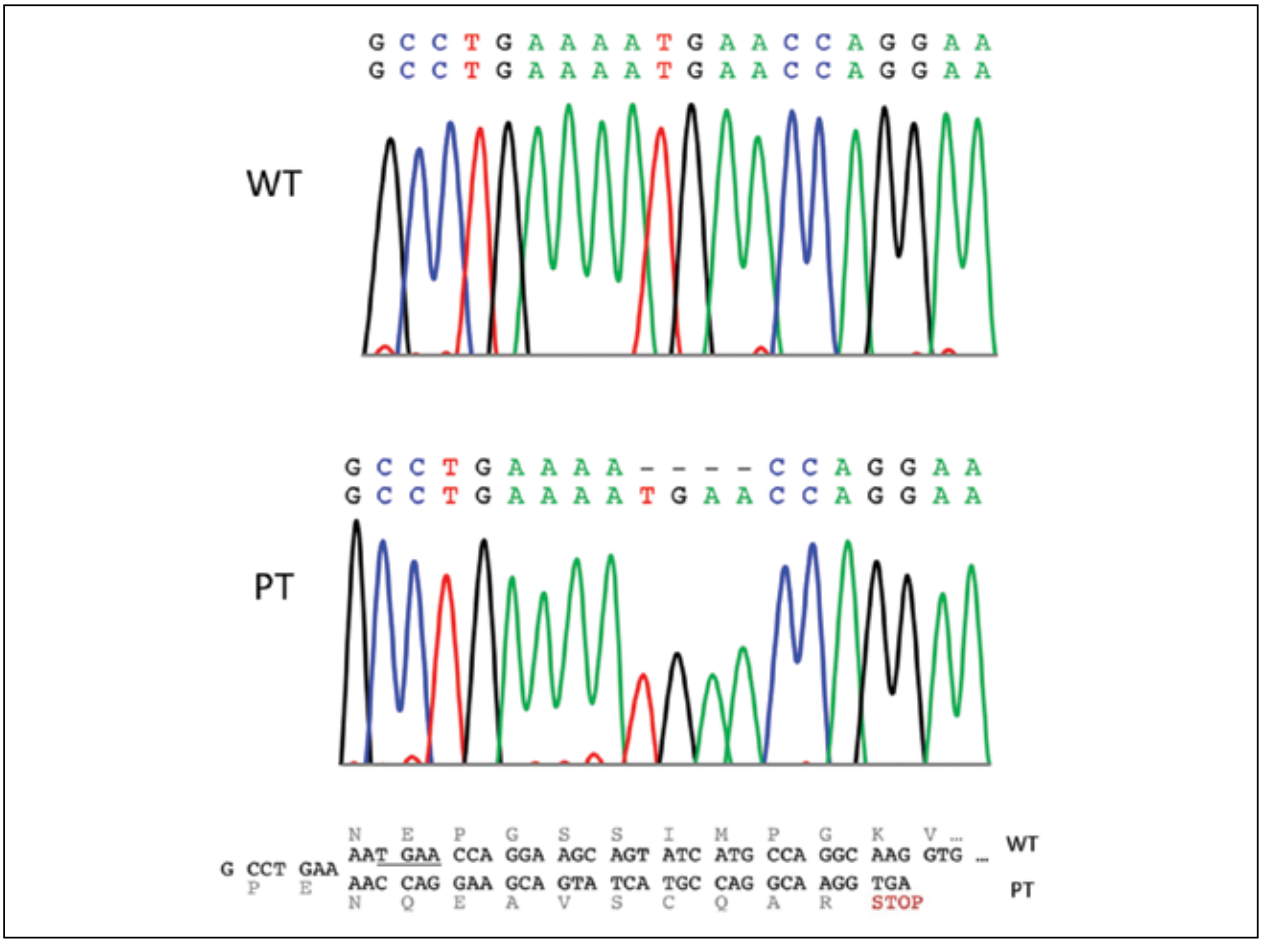


**Figure 2.** Sequencing analysis of the fumarate hydratase gene. DNA chromatograms: top, wild-type (WT) control; middle, patient (PT); bottom, comparison of WT and mutant DNA and protein sequences. Each gene located on autosomes has 2 copies, both of which are amplified during DNA sequencing. The height of peaks in the chromatograms represents the sum of nucleotides from both the copies. In this case (PT), there is a heterozygous c.1083_1086delTGAA 4-base pair deletion (TGAA deleted at positions 1083 through 1086 [complementary DNA]) in one copy and therefore the respective peak heights are reduced by approximately half compared to the WT. This deletion (underlined in bottom panel) leads to a frameshift in the coding sequence, resulting in altered amino acid sequence and a premature stop codon 10 codons downstream of the deletion, and thus a truncated protein.

benign smooth muscle proliferation expanding the reticular dermis, consistent with a cutaneous leiomyoma (Figure 1B).

Based on the clinical presentation, the possibility of HLRCCS was raised. Subsequently, the FH gene was sequenced from the peripheral blood revealing a heterozygous 4-base pair frameshift deletion mutation (TGAA deleted at positions 1083 through 1086 [complementary DNA][c.1083_1086delTGAA]), confirming the diagnosis (Figure 2). There was no family history of leiomyomata of the skin or uterus or renal tumors. Therefore, this case represents sporadic HLRCCS. Magnetic resonance imaging revealed only a 0.4-cm renal cortical cyst for which he was monitored for approximately a year but was lost to follow-up.

The molecular mechanism of tumorigenesis in HLRCCS is poorly understood.[6] Under normal circumstances, hypoxia-inducible factor (HIF) is hydroxylated by HIF prolyl hydroxylase after which it is targeted for an ubiquitin-mediated degradation (Figure 3 [top panel]). In the absence of FH, there is accumulation of fumarate, an inhibitor of HIF prolyl hydroxylase, leading to an increase in intracellular levels of unhydroxylated and undegradable HIF (Figure 3 [bottom panel]). Because of insufficient malate levels, the glucose metabolism through Krebs cycle shifts toward anaerobic glycolysis, even when sufficient oxygen is present to support respiration, creating a pseudohypoxic milieu that is similar to the Warburg effect. This environment leads to further stabilization of HIF, which

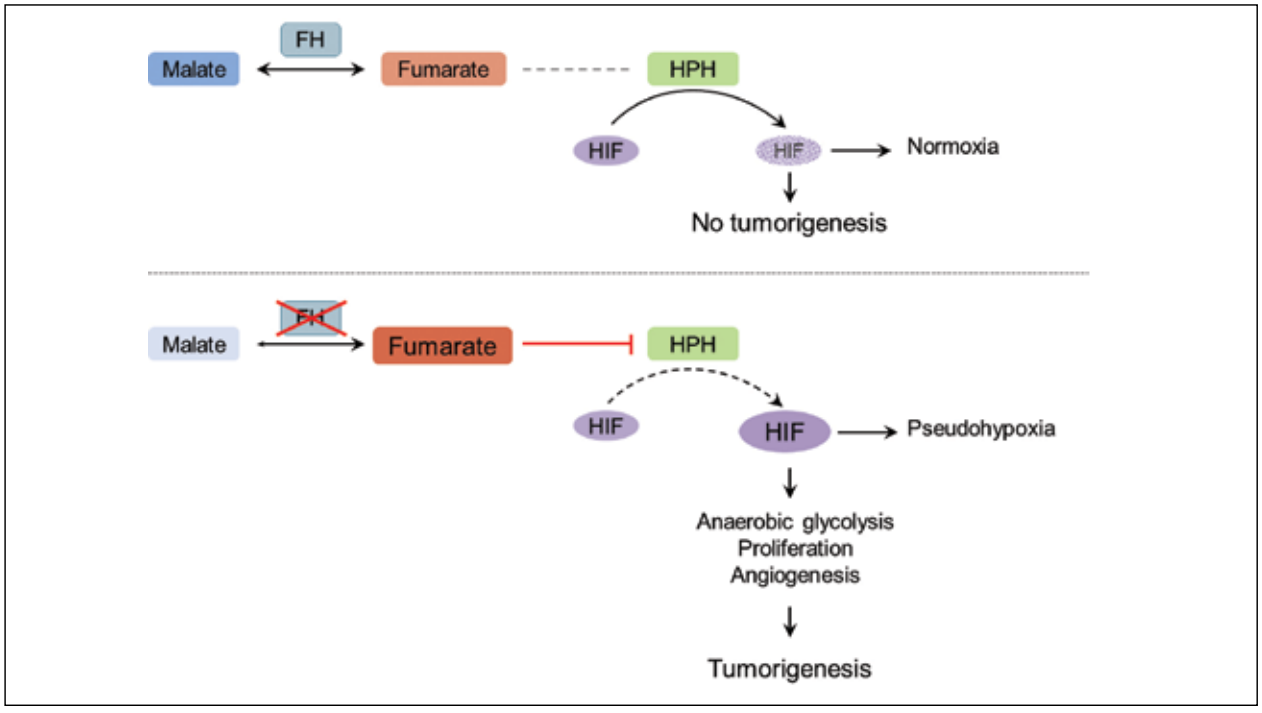


**Figure 3.** Proposed mechanism of tumorigenesis in hereditary leiomyomatosis and renal cell carcinoma syndrome. In the presence of functional fumarate hydratase (FH), hypoxia-inducible factor (HIF) is degraded, resulting in normoxia (top panel). In the absence of functional FH, there is accumulation of fumarate, while malate levels decrease, and the glucose metabolism through Krebs cycle shifts toward anaerobic glycolysis, even when sufficient oxygen is present to support respiration (bottom panel). Increased fumarate inhibits HIF prolyl hydroxylase (HPH), which leads to stabilization of HIF, a transcription factor, that enhances anaerobic glycolysis, cellular proliferation, and angiogenesis, leading to tumor growth.

is a transcription factor, that upregulates the expression of angiogenic factors (eg, vascular endothelial growth factor), growth factors (eg, erythropoietin, transforming growth factor α, platelet-derived growth factor), glucose transporters (eg, glucose transporter 1), and glycolytic enzymes (eg, phosphokinase mutase 1, lactate dehydrogenase A). These alterations may favor tumor growth by increasing the availability of biosynthetic intermediates needed for cellular proliferation and survival.

Patients with renal tumor–associated hereditary syndromes may present initially to dermatologists; therefore, it is important to recognize the cutaneous manifestations of these conditions because early diagnosis of renal cancer may prove to be lifesaving.

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