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Evidence for a New Fumarate Hydratase Gene Mutation in a Unilateral Type 2 Segmental Leiomyomatosis

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Key Words
Leiomyomatosis · Fumarate hydratase · Mosaicism

Abstract
Background: Multiple cutaneous and uterine leiomyomata syndrome (MCUL; MIM 150800) is a rare condition that sometimes predisposes to renal cancer. It is caused by deleterious mutations in the *fumarate hydratase (FH)* gene. In many patients, skin leiomyomas have been reported to develop according to a segmental type 1 or type 2 distribution. We report a patient showing multiple leiomyomas distributed according to a segmental type 2 distribution and covering several areas exclusively on the left side of his body. ***Objective:*** To search for a specific mutation in the *FH* gene associated with this phenotype. ***Methods:*** Genomic DNA from peripheral blood leucocytes of the proband was sequenced and screened for mutation of the *FH* gene. ***Results:*** Heterozygosity for an as yet undescribed mutation c.695delG, leading to a truncated protein p.Gly232AspfsX24, was found. ***Conclusion:*** We report a new mutation in the *FH* gene and discuss the unusual pattern of purely unilateral distribution in the present case.

Introduction

Multiple cutaneous and uterine leiomyomata syndrome (MCUL; MIM 150800) was first described in 1973 by Reed et al. [1]. It was subsequently found to be an autosomal dominant disease, characterized by the occurrence of multiple cutaneous leiomyomas – benign painful tumors originating from the erector pilorum (arrector pili) muscles – and, in women, of uterine leiomyomas. In some families, this syndrome predisposes sufferers to aggressive kidney cancer, with either type II papillary or collecting duct morphology, and as such has been described as hereditary leiomyomatosis and renal cell cancer (HLRCC; MIM 605839).

Fumarate hydratase (FH) gene heterozygote loss-of-function mutations at chromosome 1q42.1 were found to co-segregate with MCUL/HLRCC in all the families studied [2–4]. *FH* heterozygous mutations were predicted to result either in absent or truncated protein, as well as substitutions or deletions of highly conserved amino acids [5]. FH is an enzyme of the tricarboxylic acid cycle, involved in fundamental cellular energy production. Evidence suggests a link between defects of energy metabolism, such as in FH deficiency, and tumorigenesis [6, 7].

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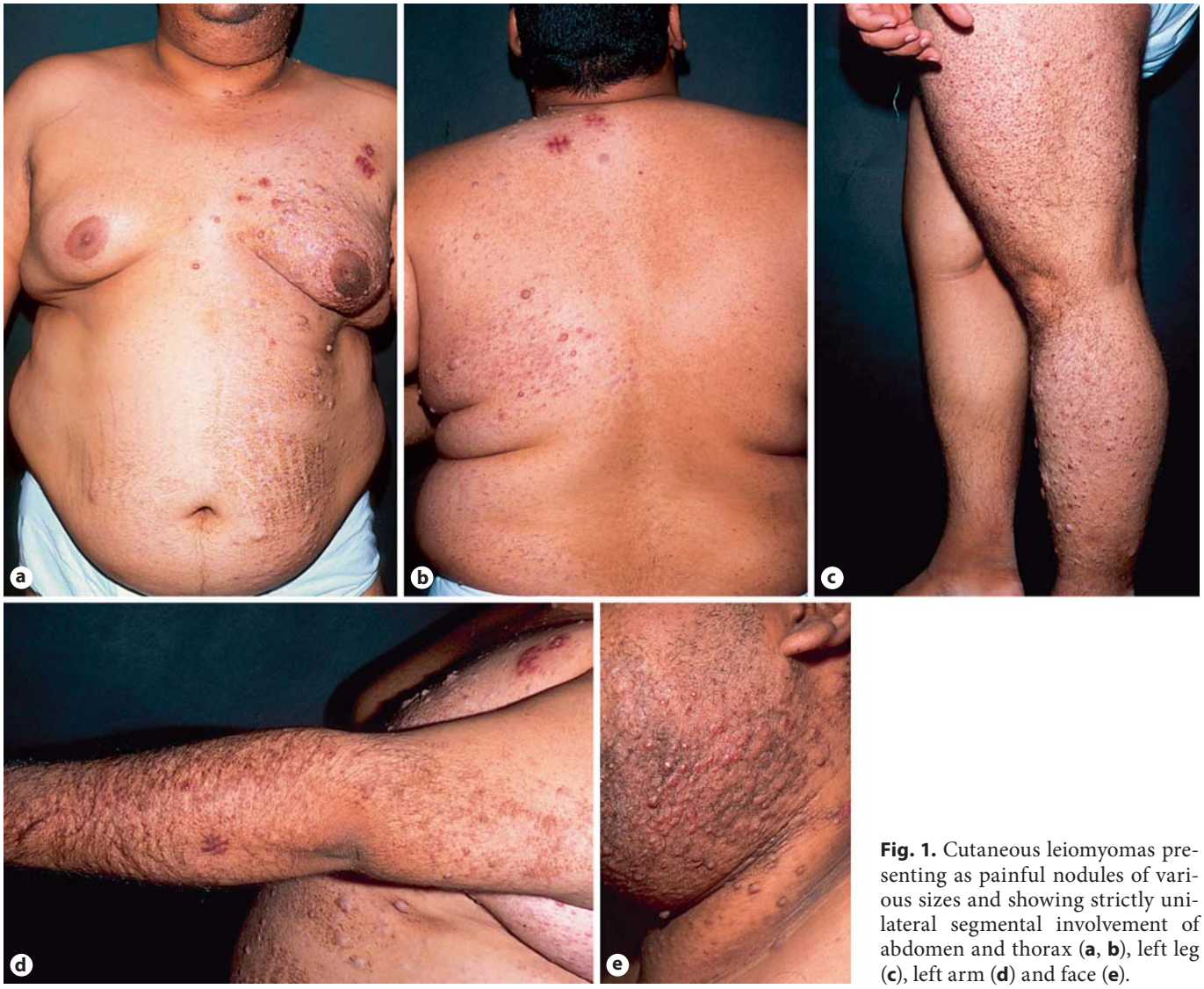

Fig. 1. Cutaneous leiomyomas presenting as painful nodules of various sizes and showing strictly unilateral segmental involvement of abdomen and thorax (**a**, **b**), left leg (**c**), left arm (**d**) and face (**e**).

In MCUL, FH is likely to act as a tumor suppressor. Its activity is very low or absent in tumors from individuals with leiomyomatosis, probably owing to a Knudson two-hit mechanism.

By analogy to other autosomal dominant skin diseases, cutaneous leiomyomas in MCUL are likely to manifest in a mosaic form. The body is involved in a linear, patchy or otherwise circumscribed arrangement. Happle [8] proposes the distinction between type 1 segmental involvement, where the segmental lesions show the same severity as in the non-mosaic trait, and type 2 segmental manifestation, where the intensity of involvement observed in the circumscribed area is far more pronounced. There are several reports of cutaneous leiomyomatosis presenting with this type 2 segmental distribution [9–12]. Together with the above-mentioned hypothesis of a two-hit model of tumorigenesis, this strongly suggests that loss of heterozygosity at the *FH* locus in the involved skin is due to a second event occurring at a post-zygotic stage. This particular form of mosaicism has been proven at the molecular level in a case of segmental Hailey-Hailey disease, which is a non-neoplastic skin disorder [13].

In the present case, we report a type 2 segmental leiomyomatosis strictly limited to one side of the body. *FH* gene sequencing of DNA from blood leucocytes revealed a novel *FH* mutation. The mechanism underlying the restriction of the disease to one body side is further discussed.

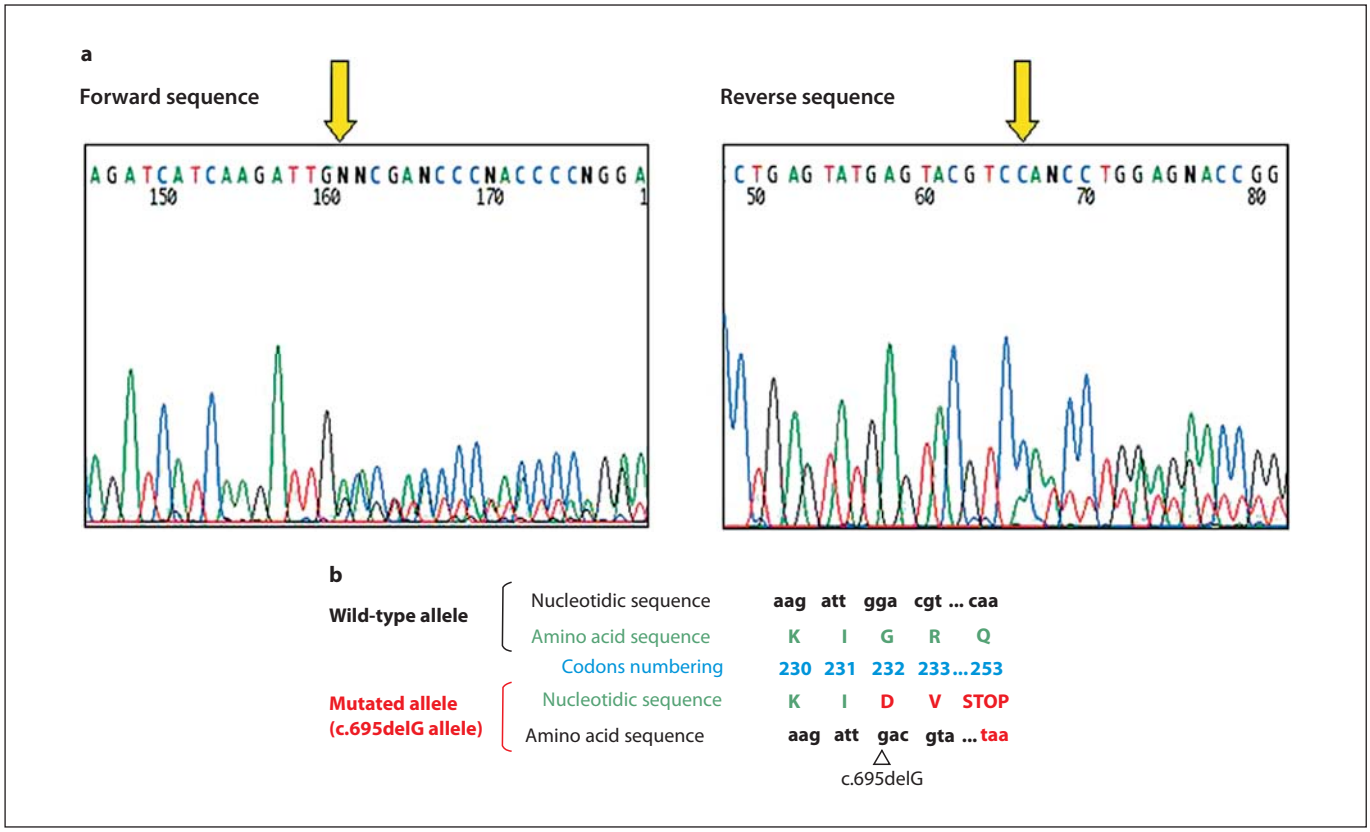

Fig. 2. a Strands of nucleotide sequences and the c.695delG (yellow arrow). **b** Abridged nucleotide and amino acid sequences of the wild-type and c.695delG allele in our patient, focused on the site of mutation. The guanine deletion in position +695 leads to both an amino acid substitution of the very conserved 232 arginine residue and to a stop codon 24 amino acids downstream. The altered amino acid sequence is highlighted in red.

Patient and Methods

A 27-year-old man from Libya was admitted to our clinic for evaluation of acquired multiple painful cutaneous tumors. The first lesions appeared on his left arm when the patient was 14 years old. Subsequently, new tumors developed on the left parts of the face, the trunk and the left leg. On physical examination, we observed hundreds of flesh-colored erythematous papulonodules. Their size ranged from a few millimeters to a few centimeters, and they were exclusively located on the left side of the body, showing a strict midline separation (fig. 1a, b). Careful examination disclosed that tumors predominated on the left arm, left leg and left side of the head, and were arranged in a segmental pattern (fig. 1c–e). The same was also observed on the trunk (fig. 1a, b). Light microscopy studies of a biopsy specimen obtained from the left arm revealed a well-demarcated tumor consisting of interlacing bundles of smooth muscle fibers. These cells stained positive for α-actin and desmin, confirming the clinical diagnosis of leiomyoma.

Clinical workup including abdominal CT scanning did not reveal evidence of a renal tumor. We were not able to examine the other family members, but according to the family history, his father had similar painful lesions on his face, neck and arms. None of his siblings exhibited similar lesions, but one sister had been treated for renal cancer. There was no other family history of cancer or uterine leiomyoma. The patient was treated by carbon dioxide laser to ablate the most disturbing and painful lesions, with a good functional and cosmetic result at 3 months. He was informed about the increased risk of developing kidney cancer and advised to have regular clinical screenings. As no official guidelines exist and since renal carcinoma in the context of MCUL syndrome behaves aggressively, we follow the recommendation of Badeloe and Frank [14] to perform systematic abdominal CT scans regularly. With regards to his relatives, all of whom were living abroad, the need for them to have an extensive clinical workup, genetic counseling and testing was explained. Unfortunately, he was quickly lost to follow-up.

With both the clinical presentation of the patient and the family history being suggestive of MCUL syndrome, we screened the *FH* gene for a mutation. Genomic DNA was first extracted from peripheral blood mononuclear cells. All exonic regions were PCR-amplified by means of a set of PCR primers as previously described [2], and subsequently directly sequenced in both directions with the Big Dye Terminator Cycle Sequencing Kit (PE Applied Biosystems, Foster City, Calif., USA).

Results

Nucleotide variation was numbered according to the Locus NM_00143 reference sequence and, in general and for the sake of clarity, we used the *FH* mutation database harmonized numbering [5]. A heterozygous 1-base deletion of nucleotide G was found at position +695 (c.695delG) of the genomic DNA sequence (fig. 2a). Extrapolating the protein translation of the mutated allele revealed a premature stop codon 24 amino acids downstream – p.Gly232AspfsX24 (fig. 2b). Unfortunately, we were not able to obtain DNA samples from other family members.

Discussion

We report an unusual unilateral systematized manifestation of the hereditary MCUL syndrome and describe a new mutation in the *FH* gene.

There are around 70 different heterozygous mutations of the *FH* gene in MCUL/HLRCC syndrome reported in the *FH* mutation database [5]. The c.695delG mutant and the resulting truncated protein have so far not been described. Although we were not able to measure FH activity in our patient, p.Gly232AspfsX24 is likely to be nonfunctional. All truncation mutants in both MCUL and HLRCC occurring downstream of the 252th amino acid have been linked to significantly decreased FH activity [2–5, 15, 16]. Moreover, the frameshift induced by c.695delG induces an amino acid change in the critical arginine 233 in which all missense mutations reported thus far (R233C, R233H and R233L) have induced a decreased activity of FH. All these arguments lead to the conclusion that transmission of the c.695delG allele was responsible for the MCUL in our patient.

The systematized segmental pattern of distribution of leiomyomas is consistent with former descriptions of the type 2 manifestation of autosomal dominant skin diseases. A similar segmental involvement has already been described in MCUL [14, 16], as well as in other skin conditions [17–25]. The type 2 is likely to reflect a second mutational event leading to loss of heterozygosity in a heterozygous embryo. The phenotype is therefore present or at least more pronounced within the skin segment having lost the corresponding wild-type allele. Conversely, in type 1, heterozygosity of a post-zygotic mutation leads to segmental involvement with a degree of severity comparable to that of the non-mosaic disorder. In the present case, a type 2 segmental manifestation is very likely for the following reasons: (1) the leiomyomas developed rather early in life; (2) they showed a rather pronounced degree of involvement; (3) the patient's father had similar skin tumors, presumably in a non-segmental form; (4) the patient had a sister who was treated for renal cancer. Hence, it is very likely that the patient will develop some additional non-segmental leiomyomas later in life.

The most striking aspect is the unilateral involvement. Thus far, such extensive lateralized involvement has rather rarely been reported in genodermatoses showing a type 2 segmental manifestation [11, 22]. If the family story is reliable, the hypothesis of a de novo heterozygous post-zygotic mutation with subsequent second mutational events is unlikely. Unfortunately, we were unable to examine the family members and confirm the anamnesis, let alone screen them for the c.695delG mutation. Conversely, assuming that the mutated allele had been transmitted from the father, occurrence of skin tumors on one side of the body would have required a second post-zygotic mutational event occurring at an early developmental stage. Validating this last hypothesis is a tough task: it implies sequencing the *FH* gene in affected and unaffected skin samples from both sides of the body together with c.695delG screening in genomic blood DNA of all family members. Unfortunately, with no further access to patients and biological material, we are now technically unable to start such a project.

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