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LETTER TO THE EDITOR

Hereditary multiple cutaneous leiomyoma resulting from novel mutations in the *fumarate hydratase* gene

KEYWORDS
Leiomyoma; Fumarate hydratase; Hereditary multiple leiomyoma of the skin; Multiple cutaneous and uterine leiomyoma

To the Editor,

Familial cutaneous leiomyomatosis is an autosomal dominantly inherited disorder characterized by disseminated leiomyoma of the skin. When associated with uterine leiomyoma it is referred to as multiple cutaneous and uterine leiomyoma (MCUL; OMIM 150800). Both disease variants result from heterozygous germline mutations in the *fumarate hydratase* (*FH*) gene [1]. This gene codes for FH, which catalyzes the conversion of fumarate to malate in the Krebs cycle and supposedly functions as tumor suppressor [1,2].

Here, we report on two individuals with cutaneous leiomyomatosis resulting from novel missense mutations in the *FH* gene. The first patient (individual III-2 in Fig. 1a) is an otherwise healthy 35-year-old British Caucasian male who developed erythematous papules on his back and left leg in 2002 (Fig. 1b). His mother (individual II-2 in Fig. 1a) underwent hysterectomy for unknown reason at the age of 30 and his grandmother (individual I-2 in Fig. 1a) had a kidney removed for polyps at early age. The second patient (individual II-2 in Fig. 1d) is a healthy 40-year-old Dutch Caucasian male who developed painful skin tumors on the left shoulder at the age of 14, which subsequently spread out to his left arm, chest, and both legs (Fig. 1e). His mother (individual I-2 in Fig. 1d) was known with uterine and cutaneous leiomyoma and his older brother (individual II-1 in Fig. 1d) also had cutaneous leiomyoma. Histopathologic examination confirmed the diagnosis of cutaneous leiomyomatosis.

We extracted genomic DNA and amplified by polymerase chain reaction (PCR) the coding regions and exon—intron boundaries of the *FH* gene using primer pairs and conditions that were described previously [3]. PCR products were purified with ExoSAP-IT (BioLynx Inc., Brockville, Ontario, Canada) and sequenced directly on an ABI 377 genetic analyzer from Applied Biosystems Inc., using the BigDye deoxy terminator V3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA). Sequence analysis was performed with the software tools Phred, Phrap and Consed, as described previously [3]. Subsequently, we used the SWISS-MODEL, a protein modeling server (http://swissmodel.expasy.org/), to localize the new mutations in the predicted 3D-structure of the human FH enzyme [4].

Sequencing analysis in the first patient (individual III-2 in Fig. 1a) revealed a heterozygous T-to-C transition at nucleotide position 1103 of the *FH* cDNA. This sequence deviation in exon 7 of the *FH* gene leads to the substitution of a methionine by a threonine residue, designated M368T (Fig. 1c). In the second patient (individual II-2 in Fig. 1d), we found a T-to-G transversion at nucleotide position 1002 of the *FH* cDNA, also located in exon 7 of the *FH* gene and resulting in the conversion of a serine to an arginine residue, designated S334R (Fig. 1f). Both sequence deviations were absent in 100 control individuals. Our nucleotide numbering for mutation designation includes the first 129 nucleotides of exon 1, the mitochondrial form of the *FH* gene, in accordance with guidelines for the description of changes in DNA and protein sequences suggested by the Nomenclature Working Group [5]. Hence, nomenclature may differ from previous reports of other authors.

Three lines of evidence suggest that the new mutations c.1103T > C,p.M368T and c.1002T > G,p.S334R are pathogenic. First, the sequence deviations could not be detected in 100 control individuals, thereby excluding a common polymorphism. Second, they cause amino acid conversions in which the side chains change in hydrophobicity or charge (M368T, a non-polar methionine to an uncharged polar threo-

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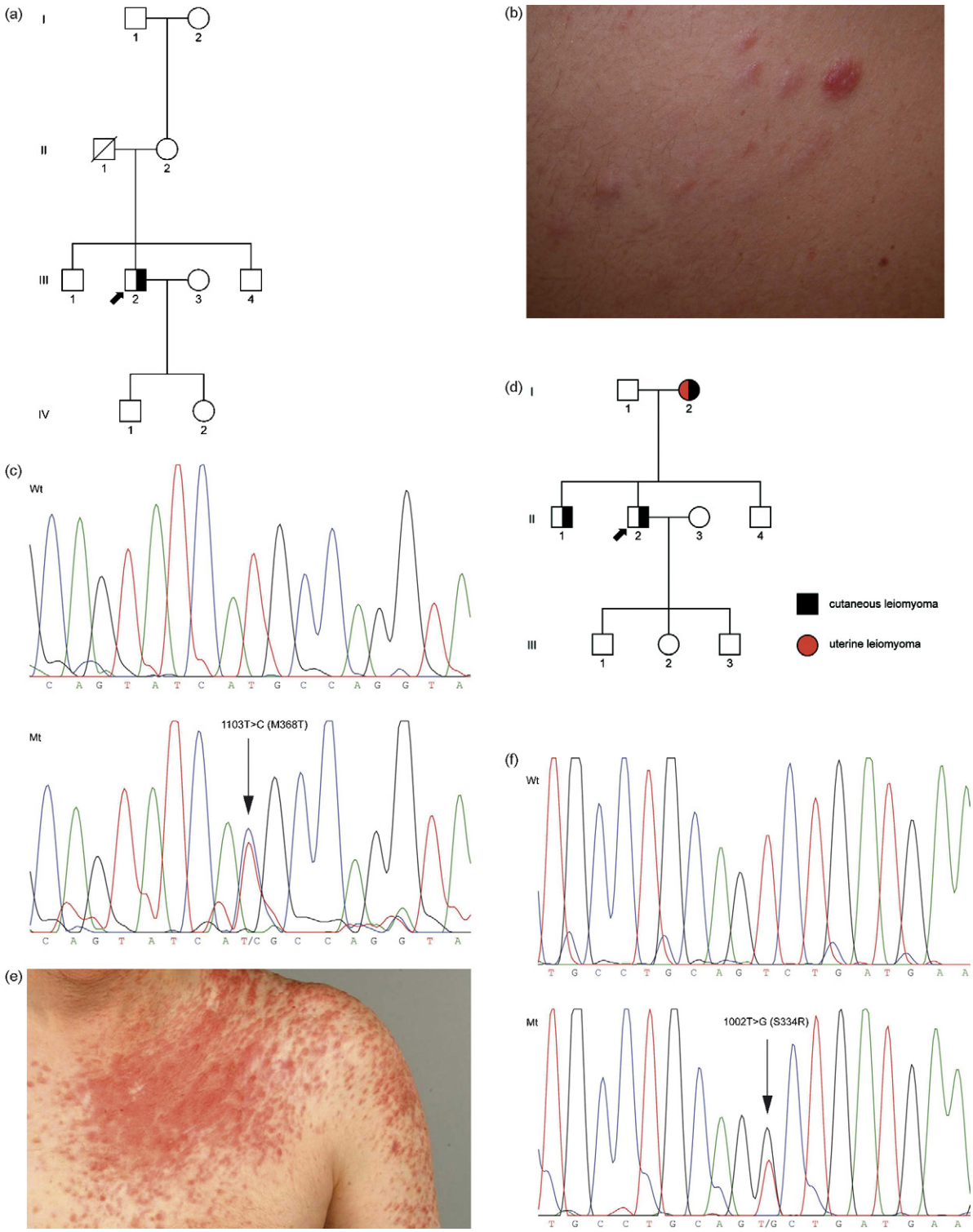

Fig. 1 (a) Pedigree of family 1. The index patient (individual III-2) is depicted with a black symbol and an arrow; (b) firm skin-colored to erythematous papules on the left back of individual III-2; (c) results of mutation analysis in individual III-2. Missense mutation M368T in exon 7 of the *FH* gene, consisting of a heterozygous T-to-C transition (arrow; lower panel), compared to the wild-type sequence of a control individual (top panel); (d) pedigree of family 2. The three individuals affected with cutaneous leiomyoma are depicted with black symbols. Note that individual I-2 also had a history of uterine leiomyoma indicated by a red symbol; (e) segmentally distributed erythematous papules and nodules on the left shoulder and chest of individual II-2; (f) results of mutation analysis in individual II-2. Missense mutation S334R in exon 7 of the *FH* gene, consisting of a heterozygous T-to-G transversion (arrow: lower panel), compared to the wild-type sequence of a control individual (top panel).

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