

# How a woman's myomectomy saved her father's life: evidence of fumarate hydratase-deficient uterine leiomyoma and early detection of germline variants in fumarate hydratase

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**Objective:** To describe a case of a personal and family history of early uterine leiomyomatosis that revealed a pathogenic variant in the *FH* gene encoding fumarate hydratase. After the patient's diagnosis, a first-degree relative was detected with early-stage renal cell carcinoma. The patient decided to undergo preimplantation genetic testing to reduce the risk to her future children.

**Design:** A case report of autosomal dominant hereditary leiomyomatosis and renal cell cancer syndrome where the patient underwent 2 cycles of in vitro fertilization with preimplantation genetic testing for monogenic disease/aneuploidy (PGT-MA) that resulted in 3 unaffected, euploid embryos.

**Setting:** Large academic single-center hospital.

**Patient(s):** A 35-year-old nulligravida woman with a personal history of an early-onset uterine leiomyomatosis and a family history of renal cell carcinoma and uterine leiomyomas, who is heterozygous for a pathogenic variant in *FH* and diagnosed with hereditary leiomyomatosis and renal cell cancer syndrome. Informed consent was obtained.

**Intervention(s):** Two laparoscopic myomectomies were performed, and tissue was sent for histopathology and immunostaining. Hereditary leiomyomatosis and renal cell cancer syndrome was confirmed by germline testing, and 2 cycles of PGT-MA were performed.

**Main Outcome Measure(s):** Through PGT-MA, the patient was able to mitigate the risk of passing a known familial variant to her future children.

**Result(s):** After 2 cycles of in vitro fertilization with PGT-MA, 3 unaffected embryos were available for transfer. An unaffected, euploid embryo was transferred for pregnancy, and the patient is currently pregnant in her second trimester.

**Conclusion(s):** Pathogenic variants in *FH* should be suspected in patients with early-onset uterine leiomyomas and a family history of cutaneous and/or uterine leiomyomas. Familial variant testing is crucial in identifying relatives at risk to start early screening. (*Fertil Steril Rep*® 2022;3:26–31. ©2021 by American Society for Reproductive Medicine.)

**Key Words:** Fumarate hydratase, uterine leiomyoma, renal cell carcinoma, preimplantation genetic testing

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**U**terine leiomyomas, also known as uterine fibroids, are benign tumors of the smooth muscle. They are the most common tumors in women of reproductive age. The lifetime incidence is estimated to be approximately 70% in the general population by the age of 50 years (1, 2). Uterine leiomyomas often occur sporadically, and most of them are chromosomally normal (3). However, somatic cytogenetic abnormalities are observed in approximately 40% of uterine leiomyomas (3). The most common aberrations observed are deletions of the long arm of chromosome 7 (7q), rearrangements involving 12q15 or 6p21, and translocations involving the long arms of chromosome 12 and 14. Somatic genetic variants have also been documented by exome sequencing. *MED12* is the most frequently mutated gene in up to 70% of uterine fibroids (3, 4). In addition to somatic changes, germline pathogenic variants in *FH* have been associated with an increased risk of early-onset uterine leiomyomas (5, 6).

Fumarate hydratase (OMIM 136850) or fumarase is an important enzyme of the tricarboxylic acid cycle, also known as the Krebs cycle. This enzyme is responsible for the conversion of fumarate to malate. *FH* is located on the long arm of chromosome 1 in band q43. Biallelic germline pathogenic variants on this gene have been associated with fumarate hydratase deficiency, also known as fumaric aciduria. Patients can present with neonatal/infantile encephalopathy characterized by failure to thrive, hypotonia, lethargy, and seizures (7).

Heterozygous germline pathogenic variants in *FH* are associated with an increased risk of autosomal dominant hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. Hereditary leiomyomatosis and renal cell cancer is a hereditary predisposition syndrome associated with an increased risk of cutaneous and uterine leiomyomas and other cancers. Pathogenic variants cause loss of function of this gene and can lead to benign skin tumors, uterine leiomyomas, and an increased risk of papillary type II renal cell carcinoma, with the expected mean age of occurrence at 30, 30, and 40 years, respectively (8). These renal tumors are typically unilateral, aggressive, and associated with poor survival due to propensity to metastasize (8). Sporadic loss of *FH* has also been reported in other tumor types such as pheochromocytomas, paragangliomas, adrenocortical carcinoma, neuroblastomas, ependymoma, osteosarcoma, and Ewing's sarcoma (9).

Uterine fibroids are common in the general population, with up to 40% of patients having symptoms (1, 2). Women with HLRCC syndrome typically present with uterine leiomyomas that are numerous and large. These women are diagnosed between 18 and 53 years of age and experience symptoms such as irregular or heavy menstrual bleeding and pelvic pain (2, 8). In fact, women with HLRCC syndrome will require early medical/surgical management compared with those with fibroids not associated with HLRCC (8).

## CASE REPORT

The patient provided informed consent to review and publish her case. We report the case of a 35-year-old nulligravida

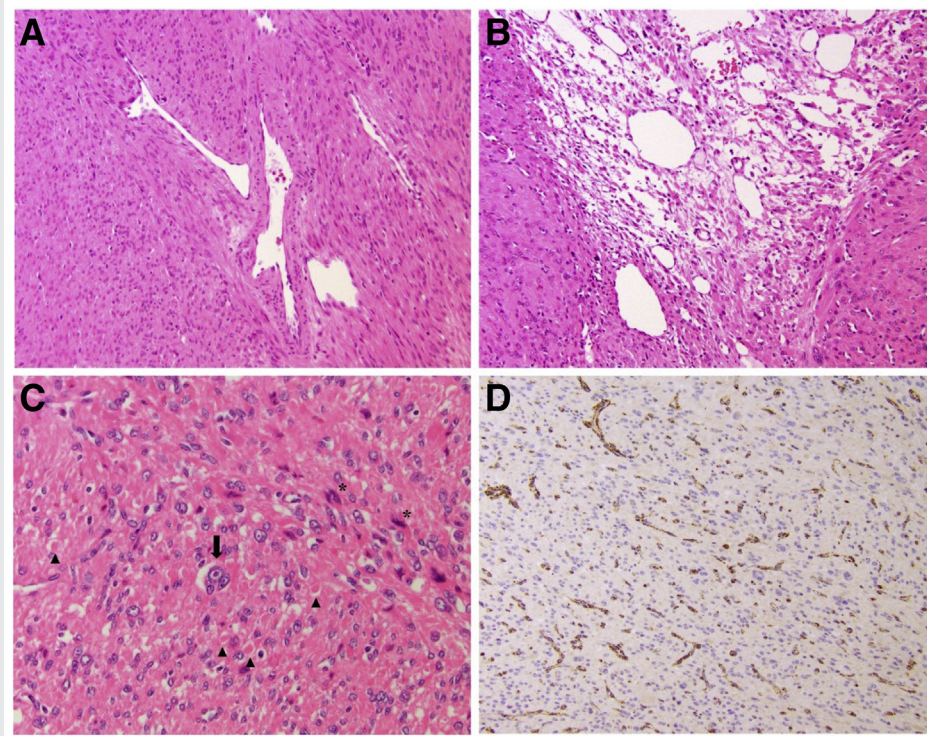
woman of Italian-Irish ancestry with a medical history of hypothyroidism and early-onset uterine leiomyomas. Her history of uterine fibroids started in her early twenties when she experienced dysmenorrhea and heavy menstrual bleeding. As part of her workup, she had an ultrasound that showed the presence of uterine fibroids. She was initially treated with over-the-counter pain medications and had a trial of oral contraceptive pills. During her mid-twenties, her symptoms started to worsen, and a progesterone intrauterine device was placed, providing some relief. After a few years, despite the progesterone intrauterine device, she became more symptomatic with dyspareunia, intermittent vaginal bleeding, and severe dysmenorrhea. A pelvic magnetic resonance imaging (MRI) showed multiple intramural leiomyomas of various sizes, the largest measuring 5.5 cm in greatest diameter. Various treatment options were presented, and she opted for a laparoscopic myomectomy for the removal of 9 fibroids.

Gross examination revealed multiple fragments of tan, whorled nodules. On microscopic examination, the leiomyomas displayed areas with increased cellularity, hemangiopericytoma-like vessels (Fig. 1A), and multiple foci with alveolar-type edema (Fig. 1B). Many cells had large nuclei with prominent cherry-red nucleoli, perinucleolar halos (Fig. 1C), and scattered cells with degenerative atypia. Eosinophilic inclusions in the background were also seen (Fig. 1C). These morphologic findings were suggestive of a diagnosis of fumarate hydratase-deficient leiomyomas. Fumarate hydratase immunohistochemistry was performed, which confirmed the diagnosis by showing the loss of expression in tumor cells (Fig. 1D) in contrast to retained expression in endothelial cells.

On evaluating her family history it was noted that an older sister was diagnosed with uterine leiomyomas at age 20. This sister underwent a myomectomy and subsequently had a hysterectomy at 40 years of age. Given the pathologic findings and the family history of early-onset uterine leiomyomas in her sister, there was a concern for HLRCC syndrome. The patient underwent germline testing that showed a pathogenic variant in *FH* (c.301 C>T, p.Arg10\*) consistent with a diagnosis of autosomal dominant HLRCC syndrome. Considering these results, her first-degree relatives were counseled and recommended for targeted variant testing. Familial testing showed that her oldest sister and her younger brother carry the pathogenic variant. Two middle sisters tested negative for the *FH* variant. Parental testing confirmed that this variant was inherited from their father (Fig. 2). These genetic test results prompted screening the patient's father with a renal ultrasound, given the associated increased risk of renal cancer. An early diagnosis of clear cell renal carcinoma was made, for which he was successfully treated with surgery and chemotherapy and is currently in remission.

Although her family was dealing with their father's recent cancer diagnosis and treatment, the patient started to plan her family. Considering the possible risk of autosomal recessive fumaric aciduria, gene sequencing for *FH* was recommended for her partner, who tested negative. The couple decided to start the process of in vitro fertilization with preimplantation

## FIGURE 1



Fumarate hydratase-deficient leiomyoma. Hemangiopericytoma-like (staghorn) vessels area easily identified (A); multiple foci show alveolar-type edema (B). Many tumor cells have large nuclei with prominent cherry-red nucleoli and perinucleolar halos (arrow). Eosinophilic inclusions are present in the background (arrowheads). Scattered multinucleated cells were observed with degenerative atypia (asterisk) (C). Fumarate hydratase immunostain shows loss of staining in tumor cells; note the endothelial cells with retained staining as an internal control (D).

Rivera-Cruz. Germline variants in fumarate hydratase. *Fertil Steril Rep* 2022.

genetic testing for monogenic disease/aneuploidy. The couple's first cycle resulted in 3 fertilized embryos and only 1 high-quality blastocyst that met the criteria for biopsy. Unfortunately, this was an affected embryo. A second cycle took place 6 months later and resulted in 7 biopsied embryos, of which 3 were both unaffected and euploid.

Before her planned embryo transfer, repeat pelvic and abdominal MRIs showed, once again, multiple intramural leiomyomas, the largest measuring 4 cm in greatest diameter. They were impacting the endometrial cavity, consistent with the known aggressive nature of these benign leiomyomas in patients with HLRCC syndrome (Fig. 3). Her kidneys were reported as normal. The patient underwent a second myomectomy before her embryo transfer. The pathology report confirmed the prior histologic and immunostaining findings. Five months after her surgery, a single unaffected euploid embryo was transferred for pregnancy. The patient is currently pregnant in her second trimester at the time of writing this report. Prenatal screening showed low-risk noninvasive prenatal testing and normal fetal anatomy scan, both of which are reassuring.

## DISCUSSION

Heterozygous pathogenic variants in *FH* have been associated with *FH* predisposition syndrome, also known as HLRCC syndrome, which increases the risk of uterine, skin, and other types of tumors, including renal cell carcinoma. We report a case of a familial pathogenic variant in *FH* consistent with the diagnosis of autosomal dominant HLRCC syndrome after the patient's first myomectomy and histological suspicion of fumarate hydratase deficiency. This subsequently resulted in risk assessment of her relatives, of which 2 siblings and their father tested positive for the variant.

In this family, HLRCC syndrome presented with early-onset uterine leiomyomatosis in 2 sisters in their twenties. Given their father's positive result, he was screened for renal tumors and was found to have clear cell carcinoma of the kidney. Clear cell histology has been previously reported in patients with HLRCC syndrome (10). Unfortunately, most of the renal tumors are metastatic or rapidly become metastatic at diagnosis (8, 10). However, in this case, the patient's father was able to have early detection and treatment and is now in remission.

FIGURE 2

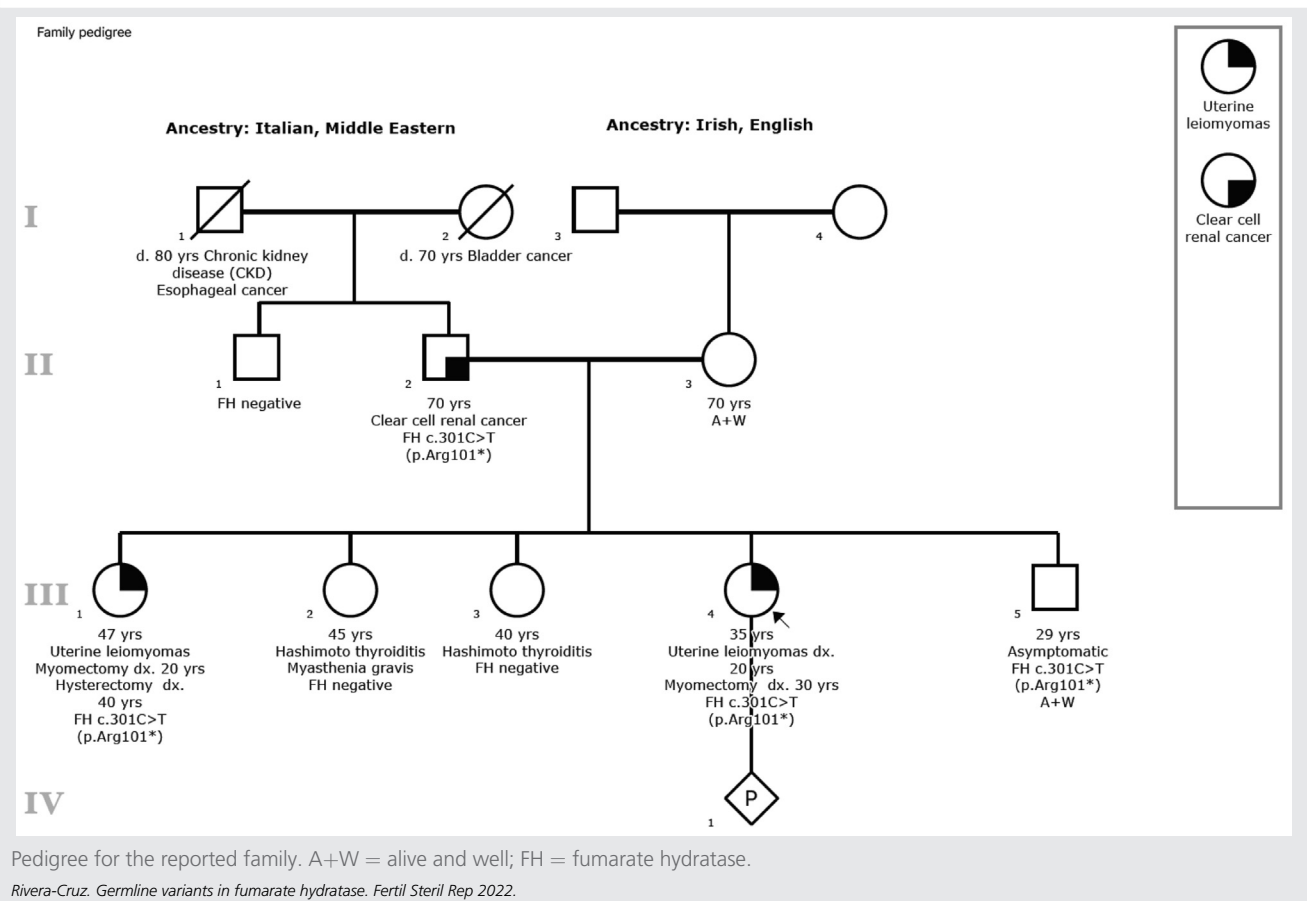
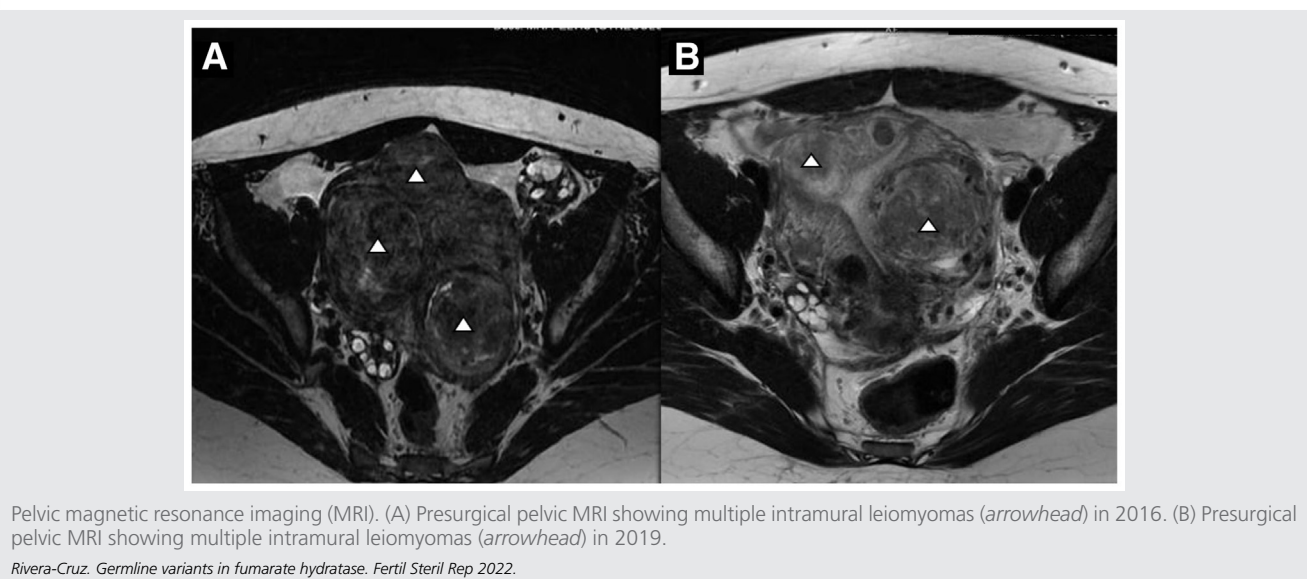


FIGURE 3



Several patients with HLRCC syndrome have been described in the literature with the same pathogenic variant identified in this family (*FH* gene, c.301C>T, p.Arg101\*). This genetic change results in the loss of normal protein function and is interpreted as a disease-causing variant. This variant is a recognized founder variant reported in England and Germany attributed to a Polish ancestor. However, no correlation has been observed between specific *FH* pathogenic variants and the occurrence of cutaneous lesions, uterine fibroids, or renal cancer (11).

Fumarate hydratase-deficient leiomyomas have been previously reported in approximately 1.4% of women with uterine leiomyomas (8). Most fumarate hydratase-deficient leiomyomas tend to occur sporadically and are not associated with HLRCC syndrome (5). However, considering the family history, germline testing can aid in identifying pathogenic variants in *FH*. From a pathology standpoint, certain morphologic features of leiomyomas, including increased cellularity, hemangiopericytoma-like vessels, alveolar-type edema, eosinophilic inclusions, tumor cells with large nuclei, prominent nucleoli and perinucleolar halos, and multinucleate cells with degenerative atypia have been shown to be associated with fumarate hydratase-deficient leiomyomas (12, 13). The identification of these features should be followed by fumarate hydratase immunohistochemistry. As this case report highlights, uterine leiomyoma histology could be used to identify individuals at risk for HLRCC syndrome (14). The loss of fumarate hydratase staining in this context is consistent with a diagnosis of fumarate hydratase-deficient leiomyoma and should prompt the evaluation of the patient's family history, followed by confirmatory germline testing. However, fumarate hydratase immunostaining can also be positive in a subset of tumors with suspicious morphology, and in an appropriate clinical setting and strong family history, patients should also be tested for *FH* pathogenic variants (5, 15).

As presented in our case, high suspicion of this syndrome is needed for appropriate preconception counseling, early screening, and surveillance. Understanding the risk for future pregnancies is important in the preconception period as partner testing is recommended due to the potential risk of autosomal recessive fumaric aciduria (8). Preimplantation genetic testing remains an option for couples interested in reducing their risk of having an affected child with HLRCC syndrome.

After receiving the diagnosis, patients should undergo a series of medical evaluations and screening with the main goal to have early detection of renal cell carcinoma (8, 10). Consensus in the pediatric population recommends screening as early as 8 years of age with abdominal imaging. Screening in adults is recommended at the time of diagnosis, followed by yearly evaluation. Abdominal imaging with MRI with contrast is the preferred method for screening. Renal ultrasound is sometimes warranted to characterize the renal lesions better (8). Medical evaluations with dermatology and gynecology are recommended. Dermatology evaluation for full skin examination is recommended every 1–2 years after the diagnosis to evaluate the extent of the lesions and to monitor changes. The gynecologic evaluation should start

around 20 years of age or earlier in women if symptoms arise (8).

## CONCLUSION

Germline *FH* variants should be considered in families with an early presentation of multiple uterine fibroids in >1 family member or a history of renal tumors. An emphasis on the patient's family history is strongly advised if the leiomyomas show morphologic features suggestive of fumarate hydratase deficiency, supported by fumarate hydratase immunohistochemistry.

By identifying the germline *FH* variants, relatives at risk can also pursue germline variant testing. Proper screening and surveillance should be started once the diagnosis is established, especially for renal tumors. The process of in vitro fertilization with preimplantation genetic testing for monogenic disease/aneuploidy is available for families who wish to reduce the risk of having an affected offspring with this syndrome.

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