ORIGINAL RESEARCH

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Variants of Fumarate Hydratase Gene in Uterine Disorders: A Clinical Trial

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ABSTRACT Objective: The dysregulation of metabolism is a hallmark of cancer. Enzymes of tricarboxylic acid (TCA) cycle have a key role in pathogenesis of carcinogenesis as oncometabolits. The variants in fumarate hydratase (FH) gene have been linked to sporadic tumors and familial tumor propensity. To asses the prevalence of variants in the FH gene in endometrial carcinoma (EC) and uterine leiomyomas (UL). **Material and Methods:** This prospective study included 58 patients with EC and 44 with UL. The FH gene variants were analyzed in the DNA samples collected from peripheral circulation. All exons of the FH gene were replicated by polymerase chain reaction utilizing specific primers including intron-exon boundaries and than was sequenced with Sanger method. **Results:** Only two variants were detected in two different patients. The c.927G>A (p.Pro309Pro) and c.63C>T (p.Ala21Ala) variants were observed in patients with UL, EC respectively. c.927G>A (p.Pro309=) and c.63C>T (p.Ala21=) are rare variants inside the overall population with allele frequency ranges of 0.02428, 0.000014 respectively. **Conclusion:** The contribution of variants in genes encoding the TCA cycle enzymes in tumor cells has provided understanding fundamental role on metabolic alterations in carcinogenesis. Further studies are needed to discover the novel tumor mutations and identify appropriate treatment.

Keywords: Endometrial cancer; fumarate hydratase; single nucleotid polymorphism; tricarboxylic acid cycle; uterine leiomyoma

The dysregulation of metabolism is a hallmark of cancer.[1] In addition to oncogenic trigger mutations, many cancers exhibit effects on cell metabolism. Many metabolic changes in cancer cells, including the Warburg effect, affect the tumor microenvironment.[2] Cancer cells are capable of continuous and uncontrolled proliferation. Due to the nutritional needs that they cannot meet normally, they go to changes through their metabolism. Glucose metabolism is the most studied and researched metabolism. Most cancer cells produce large amaounts of lactate regardless of the availability of oxygen, and this metabolism is called aerobic glycolysis. It is unclear why tumor cells would choose such an ineffective energy conversion mechanism. Although it is not believed that this impact is caused by errors in mitochondrial respiration, it is interesting that certain malignancies exhibit gene mutations that control the tricarboxylic acid (TCA) cycle, also known as the Krebs cycle or citric acid cycle, which results in an increase in its intermediate metabolites. It has been demonstrated that certain of these metabolites participate in oncogenic pathways.

The deposition of intermediate metabolites in the TCA cycle in cancer cells are concluded not only metabolic but also epigenetic alterations, which could cause epithelial to mesenchymal transition in tumor cells.[2]

Isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) are metabolic enzymes that are critical elements of the TCA cycle. These metabolites are hypothesized to have an influence on the emergence of several cancer

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syndromes via inhibiting alpha-ketoglutarate and dependent dioxygenases.[3] Because these dioxygenases involve enzymes that regulate histone hypomethylation or induce DNA demethylation, the association of tumorigenesis has been attributed to breakdown of usual epigenetic gene regulation. The methods by which FH deficiencies cause carcinogenesis are uncertain; however, they could include hypoxia pathway activation or change in citrate synthesis via the TCA cycle.[4,5]

The FH enzyme, which performs the conversion of fumarate to malate inside the TCA cycle is encoded by the *FH* gene localized at 1q42.3-43 chromosome.[6]

Homozygous or compound heterozygous mutations in *FH* gene causes fumarase insufficiency, resulting in newborn encephalopathy and a poor prognosis.[7] Whereas heterozygotes for the *FH* gene submit with signs such numerous cutaneous leiomyomas, initial uterine leiomyomas (UL), and elevated risk for papillary Type II renal cell carcinoma.[7,8]

The mutations in FH and several components of the SDH complex have been related to sporadic tumor forms and familial tumor propensity.

Uterine corpus cancer is the sixth most frequent cancer of the female genital tract system, with 417,000 new cases and 97,000 deaths worldwide while it is the most widespread female cancer in Türkiye with 5,918 new cases and 1,589 deaths in 2020.[9] Despite the fact that most cases of endometrial cancer are sporadic, some are inherited and are brought on by germline mutations, most notably those in the mismatch repair genes.[10]

UL are the far more prevalent lesions in females of fertile period. According to cytogenetic research, 40 to 50 percent of leiomyoma samples have chromosomal rearrangements, while up to 70 percent of cases have somatic mutations.[11,12] Besides acquired mutations, which may play a role in leiomyoma carcinogenesis, the only reported hereditary syndrome associated with UL is Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome. HLRCC also called Reed syndrome is an uncommon autosomal dominant genetic disease associated with germline mutations in the *FH* gene (MIM# 136850).[13]

The goal of this research was to assess the molecular alterations in the *FH* gene in common benign and malignant uterine corpus disorders, particularly endometrial cancer and UL.

MATERIAL AND METHODS

PATIENTS

This prospective study involved 58 cases with endometrial cancer and 44 with uterine leiomyoma who were operated on in our clinic between May 2019 and May 2020. Individuals with uterine leiomyoma, particularly those with fibroids greater than 5 cm in diameter were enrolled in this study. The *FH* gene mutations were analyzed in the DNA samples extracted from peripheral blood. Each patient who participated in the trial provided their informed consent. In addition to demographic details of the patients such as age, parity, additional disease history, histopathological findings, surgical procedure, the radicality of hysterectomy, lymph node dissection, International Federation of Gynecology and Obstetrics stage, and grade data were collected by the electronic documents of the center's medical records.

FH GENE MUTATION ANALYSIS

Genetic analysis was conducted at the Gazi University Faculty of Medicine Pediatric Genetics and Metabolic Diseases Laboratory in Ankara, Türkiye. DNA was isolated in the circulating leukocytes of every participant utilizing the iPrep™ PureLink gDNA Blood Kit (Invitrogen, Carlsbad, CA) according to the producer's direction.

All exons of the *FH* gene (NM_000143.4) were replicated using polymerase chain reaction (PCR) using specific probes including intron-exon boundaries. Table 1 lists the PCR product diameters and primer sequences. PCR products from all exons of the *FH* gene were purified by ExoSap-IT™ (Thermofisher, Waltham, MA, USA) protocol. All exons were sequenced by using cycle sequencing protocol (BigDye™ Terminator v3.1 Cycle Sequencing Kit, Applied Biosystems™, Thermo Fisher Scientific, USA) and run on the capillary electrophoresis (Applied Biosystems).

TABLE 1: Primers and size of PCR products used in the study.

	Forward (5' - 3')	Reverse (5' - 3')	PCR product size
Exon 1	GAATCTCTCCCGCCAAGTC	GGTCATTCACGATTGGTCCT	375 bp
Exon 2	CAAAGCGATGGCTCAAAATAA	CCTGAAAGTGAGGAAGAGAATGA	496 bp
Exon 3	TCACAGTTCCCCTTTCCTTCT	TCTTGGTTCATGAATTCCTGTCT	380 bp
Exon 4	AAGAACCATAAGAAGCCTTATCCA	TCTGTGGTTGGAGCAAGTGA	434 bp
Exon 5	CGGTTACAAATTTGGCCTTTT	GCTGGGTTTTGAGTAGTTAGTTGG	400 bp
Exon 6	CACAAGAATTCAAGACAGGAACAC	TTATCAGTGGCATTGTCGTACC	473 bp
Exon 7	CCAGCTGCGGGATAACTTT	TGGAACTTTCTGTTTCACTTGCT	393 bp
Exon 8	ACCCAACTACCCAATGTGGA	CTACCCATCCCACCTTCCTT	397 bp
Exon 9	GCTGTTCTCAAACACTGATCCA	GTGCCTTCAAATGTTCATGCT	452 bp
Exon 10	TCCATCTTAGACCTAGCACATCC	TTAAGAGGCCCATATAGCATCAA	422 bp

PCR: Polymerase chain reaction; bp: Base pairs.

STATISTICAL ANALYSIS

SPSS software (version 22.0, IBM, Armonk, New York), was used to conduct the statistical analysis. We used descriptive statistics as categorical and continuous variables. The categorical parameters were presented by number and percentage, and continuous variables were reported as mean±standard deviation for data with normal distributions and median (minimum-maximum value) for non-normal different datasets.

ETHICAL APPROVAL AND INFORMED CONSENT

The Ethics Committee of the Faculty of Medicine of Gazi University consented to the research (date: September 12, 2018, no: 01/2019-33). Written informed permission was acquired after all participants received information about the study. This research was carried out in accordance with the Helsinki Declaration principles.

RESULTS

The patient group's median age was 57 years (ranged from 36 to 78) in endometrial carcinoma (EC) and 45 years (ranged from 26 to 81) in UL cases. The demographic findings of the patients and the distribution of their complaints at presentation are presented in Table 2. Two patients in the EC group had a history of breast cancer, while three cases in the UL group had a history of thyroid papillary cancer.

The most common histology in the EC group was endometrioid type (77.6%). The final pathologic report revealed leiomyosarcoma in three of the UL cases, with tumor sizes exceeding 5 cm in all of them. The clinical and histopathological results of EC and ULs cases are presented in Table 3. Nevertheless, FH insufficiency has been consistently related to the HLRCC syndrome, neither of our

TABLE 2: Demographic characteristics of the patients with endometrial cancer and myoma uteri.

	Endometrial cancer n (%)	Uterine leiomyomas n (%)
Age (median/minimum-maximum)	57 (36-78)	45 (26-81)
Parity status		
Nulliparous	7 (12.1)	8 (18.2)
Primiparous	4 (6.9)	6 (13.6)
Multiparous	47 (81)	30 (68.2)
BMI (median/minimum-maximum)	27 (22-44)	24 (21-31)
History of disease		
None	16 (27.6)	27 (61.4)
HT	11 (19)	6 (13.6)
DM	6 (10.3)	6 (13.6)
HT+DM	20 (34.5)	-
Hypothyroidism	3 (5.2)	3 (6.8)
History of malignancy	2 (3.4)*	2 (4.5)**
Application complaint		
Routine control	1 (1.7)	-
Pelvic pain	3 (5.2)	21 (47.7)
Abnormal vaginal bleeding	11 (19)	15 (34.1)
Postmenopausal bleeding	43 (74.1)	2 (4.5)
Abdominal swelling	-	6 (13.6)
Total (patient, n)	58	44

*Breast cancer; **Thyroid papillary cancer; BMI: Body mass index; HT: Hypertension; DM: Diabetes mellitus.

TABLE 3: Clinical and histopathological results of EC and UL cases.

EC	n (%)	UL	n (%)
Histopathological features			
• Endometrioid	45 (77.6)	• UL	41 (93.2)
• Serous	7 (12.2)	• Leiomyosarcoma	3 (6.8)
• Carcinosarcoma	2 (3.4)	M<5, atypia/nec (-)	41 (93.2)
• Undifferentiated	3 (5.1)	M≥5, atypia/nec (+)	3 (6.8)
• Neuroendocrine	1 (1.7)	**Tumor size**	
Stage status		• 5-9 cm	32 (72.7)
• Stage Ia	36 (62.1)	• 10-15 cm	12 (27.3)
• Stage Ib	5 (8.6)		
• Stage II	10 (17.2)		
• Stage IIIc1	3 (5.2)		
• Stage IIIc2	4 (6.9)		
Surgical approach			
• Laparoscopy/Laparotomy	27 (46.5)/31 (53.5)		5 (11.3)/39 (88.7)
TH+BSO+Cytology	36 (62)	TH+BSO	29 (65.9)
TH+BSO+PPLND (Debulking)	22 (38)	Myomectomy	15 (34.1)
Total (case, n)	**58**		**44**

EC: Endometrial cancer; UL: Uterine leiomyomas; TH+BSO: Total hysterectomy and bilateral salpingo-oophorectomy; PPLND: Pelvic and paraaortic lymphadenectomy; M: Mitosis; Nec: Necrosis.

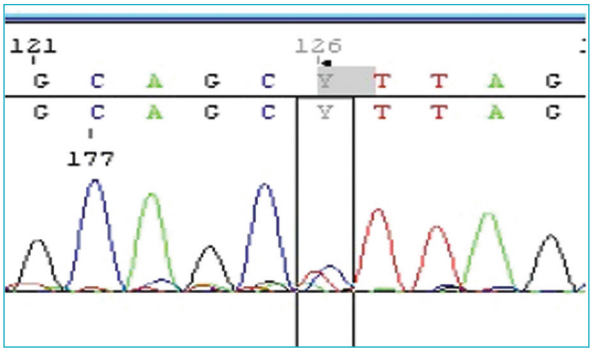

FIGURE 1: c.63C>T (p.Ala21Ala) variant is observed in a patient diagnosed endometrium cancer in Sanger sequence analysis.

patients had signs of renal malignancy and a background of inherited slightly earlier UL which could indicate HLRCC.

Only two variants were detected in two different patients (Figure 1, Figure 2). Detected variants in the *FH* gene are given in Table 4. c.927G>A (p.Pro309=) and c.63C>T (p.Ala21=) are rare variants among the overall population within allele frequencies of 0.000003984 and 0.00001692, respectively (https://gnomad.broadinstitute.org/). The patient with the c.927G>A (p.Pro309Pro) variant was 39 years old and showed non-specific UL pathologic symptoms (no mitotic, atypia, or necrosis). The case with c.63C>T (p.Ala21Ala) variant was 48 years old and observed endometrioid carcinoma with low grade and early stage.

DISCUSSION

In this study, two variants in *FH* gene were detected in two different patients. The c.927G>A

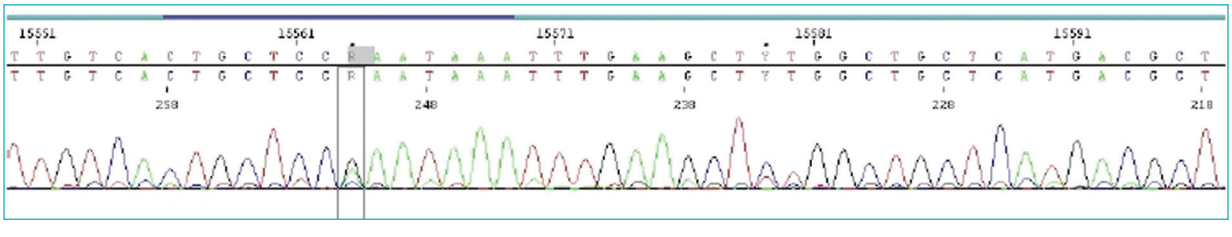

FIGURE 2: The c.927G>A (p.Pro309Pro) variant is observed in a patient diagnosed uterine leiomyoma in Sanger sequence analysis.

TABLE 4: Variants detected in FH gene.

Patient #Clinical group	c.DNA	Protein	dbSNP	Exon	Zygosity	Reference sequence [13]	Classification (According to ACMG criteria)	Classification (According to ClinVar)
EC	c.63C>T	p.Ala21Ala	rs555404867	1	Heterozygous	NM_000143.3	Likely benign (pm2, bp7, bp6)	Likely benign/Uncertain significance
UL	c.927G>A	p.Pro309Pro	rs61737760	7	Heterozygous	NM_000143.3	Benign (bp7, bs2, bp6, ba1)	Benign

FH: Fumarate hydratase; EC: Endometrial cancer; UL: Uterine leiomyomas.

(p.Pro309Pro) and c.63C>T (p.Ala21Ala) variants were observed in patients with UL, EC respectively. c.927G>A (p.Pro309=) and c.63C>T (p.Ala21=) are rare variants among the overall population within allele frequencies of 0.02428, 0.000014, respectively.

Alteration in metabolism constitute one of the characteristics of cancer.[1] Even if in the existence of oxygen, cancer cells prefer to create adenosine triphosphate through the far less efficient procedure of glycolysis rather than the highly energy-efficient process of oxidative phosphorylation, as described by the "aerobic glycolysis" (also called as the "Warburg effect").[2,14] It is unclear why tumor cells use such an ineffective energy conversion pathway. To this day, it's still unclear if aerobic glycolysis is an actual cause of cancer or merely a result of it.

The TCA cycle, which is consisted of a series of metabolic events in the mitochondrial matrix, is crucial for cellular energy production and biosynthesis of macromolecules. In the Krebs cycle, metabolic enzymes, such as IDH, SDH, and FH play critical roles.[15] It has already been shown that TCA cycle dysfunction is related to several pathological conditions.[16] FH, one of the TCA cycle intermediates, has been shown to have a remarkable relationship with hypoxia-inducible factor. The mutations in genes encoding these metabolic enzymes have potential influence in the pathogenesis of carcinogenesis not only by metabolic pathways but also via epigenetic instability.[17,18] The *FH* gene mutations induce a decrease in the function of the FH enzyme, and resulting in accumulation of fumarate substrate. Metabolic and epigenetic abnormalities are brought on by excessive fumarate values.[19] The mutations in FH and several components of the SDH complex have been related to sporadic tumor forms and familial tumor propensity.

HLRCC are caused by the mutations in the *FH* gene on chromosome 1q43. Germline FH mutations were found in approximately 60% of families segregating HLRCC.[4] FH germline mutations are observed in the HLRCC cancer predisposition syndrome, while somatic FH mutations can be found in a small subset of uterine smooth muscle tumors.

Studies proposed that variants in FH or related genes may also predispose to UL; however, it is uncommon in nonsyndromic UL or fibroids.[20] Aissani reported FH mutations in 9 out of the 18 HLRCC-related UL cases and determined two missense mutations in FH in only two nonsyndromic UL cases and one control.[20] The detection rate of FH deficiency by immunohistochemistry was 1.6% in nonatypical UL, 1.8% in cellular UL, 37.3% in atypical leiomyomas, and none in the leiomyosarcomas.[21] In our study, we did not detect mutations in the FH mutations among leiomyosarcoma patients similar to this report.

According to Miettinen, 8 of 16 FH-deficient non-atypical leiomyomas had *FH* gene mutations, involving 3 frameshift mutations and 5 entire gene deletions. The germline mutational prevalence for the *FH* gene was 2.0%. (three of 153 patients).[21] Harrison et al. determined 6 FH mutants out of 10 FH-insufficient UL, which is a similar rate in other studies; however, none of these mutations were found in the germline.[22]

The c.927G>A (p.Pro309Pro) variant was observed only one patient who showed non-specific UL pathologic symptoms (no mitotic, atypia, or necrosis) in this study. However, no germline mutations were detected. IHC testing for FH may be helpful in verifying patients at high risk for hereditary disease before genetic testing due to the comparatively high prevalence of somatic mutations. Nevertheless, the clinical value of screening unselected patients for FH-deficient leiomyomas is limited.

Advances in molecular characterization tools, such as next-generation sequencing, have recently led to a better understanding of the molecular changes that drive endometrial cancer pathogenesis. The topography of genetic mutations found in ECs has been exposed by recent developments in molecular investigations and has provided a vital perception of the etiology of this disorder.[23] This study aimed to identify the *FH* gene variants among EC cases, thus we can contribute novel treatment and follow-up strategies. We were only able to detect the c.63C>T (p.Ala21Ala) variant on the first exon in a case diagnosed endometrioid carcinoma with low grade and early stage. In previous reports, *FH* gene mutation was detected in benign lesions, such as ovarian mucinous cystadenoma and uterine myomas, but in EC in only one case.[24-26]

New therapeutic strategies for FH-insufficient renal cell cancer are being researched or evaluated in clinical trials, include the use of metformin to opposite AMP-activated protein kinase disable, include glucose carrying, and target the tumor vascular system and glucose transfer with elements such as bevacizumab and erlotinib.[23] If there is a significant prevalence of *FH* gene mutations in EC and UL cases than in the general population, this data could lead to the development of new adjuvant treatment options for patients.

One of the study's limitation is that it included nonselective patients. In this work, Sanger sequencing was performed to screen the *FH* gene in UL cases with no family history of HLCC and no immunohistochemical expression. Furthermore, the underlying mechanism of the *FH* gene in EC must be verified in the future.

CONCLUSION

In addition to the histopathological classifications of gynecological tumors, molecular assessment provides significant options for prognostic indicators and treatment management to meet our new targeted treatment requirements other than conventional medicines. In this report, two rare variations in the *FH* gene were detected, one in the EC case and the other in the UL case. The identification of mutations in genes encoding the TCA cycle enzymes in cancer cells has provided researchers a better understanding of how metabolic alterations affect cancer cells. These gene mutations have been observed in many cancer types. Further studies are needed to discover the novel mutations in kinds of tumors and to identify potential therapeutic targets.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ferah Kazancı, Fatih Süheyl Ezgü;* ***Design:*** *Ferah Kazancı, Mehmet Anıl Onan;* ***Control/Supervision:*** *Ferah Kazancı, Mehmet Anıl Onan;* ***Data Collection and/or Processing:*** *Ferah Kazancı, Dilek Yüksel;* ***Analysis and/or Interpretation:*** *Ferah Kazancı, Özlem Erdem, Fatih Süheyl Ezgü;* ***Literature Review:*** *Ferah Kazancı;* ***Writing the Article:*** *Ferah Kazancı;* ***Critical Review:*** *Mehmet Anıl Onan;* ***References and Fundings:*** *Scientific Research Projects of Gazi University;* ***Materials:*** *Ferah Kazancı.*

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