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Original Article

The spectrum of clinical and genetic findings in hereditary leiomyomatosis and renal cell cancer (HLRCC) with relevance to patient outcomes: a retrospective study from a large academic tertiary referral center

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Abstract: Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant condition attributed to pathogenic variants in *fumarate hydratase* (*FH*) and presents with cutaneous leiomyomas (CLMs), uterine leiomyomas (ULMs) and renal cell cancer (RCC). The objective of this study was to characterize the spectrum of clinical and genetic findings in HLRCC at a large academic tertiary care referral center with a focus on dermatologic manifestations. Fifty-seven patients, 41 female and 16 male, with 27 unique pathogenic or likely-pathogenic *FH* variants were identified from 38 families. Mean age of HLRCC diagnosis was 44.4 years (range 8-82). CLMs were the primary reason for referral in 49.1% (n=28). CLMs were present in 43/56 patients who underwent full skin examination. Three of these 56 patients were diagnosed with cutaneous leiomyosarcoma. Incidence of ULMs was 37/41 female patients; no uterine leiomyosarcomas were observed. RCC was observed in 6/57 patients (mean age of diagnosis: 47.3 years (range 28-79)). CLMs predated RCC in the 3 patients diagnosed with both. Dermatologists have an opportunity to recognize cutaneous manifestations of HLRCC, including cutaneous leiomyomas and rarely cutaneous leiomyosarcomas, and refer for genetic evaluation to provide definitive diagnosis. Identification of HLRCC can promote family cascade testing and screening for RCC.

Keywords: Hereditary leiomyomatosis and renal cell cancer, reed syndrome, cutaneous leiomyoma, uterine leiomyoma, renal cell cancer, cutaneous leiomyosarcoma, fumarate hydratase, genetic variants

Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC), also known as Reed Syndrome, is a tumor predisposition syndrome characterized by cutaneous leiomyomas (CLMs), uterine leiomyomas (ULMs), and renal cell carcinoma (RCC) [1, 2]. HLRCC is caused by pathogenic variants in fumarate hydratase (*FH*) and inherited in an autosomal dominant pattern with variable penetrance. *FH* encodes the enzyme that catalyzes the formation of malate from fumarate in the mitochondrial tricarboxylic acid cycle. The pathophysiology of *FH* as a tumor suppressor, however, remains poorly understood [3-6]. Cutaneous, uterine, and renal manifestations of HLRCC are well-described [7-13]. Herein, we describe a cohort of patients with HLRCC at a large academic tertiary referral center to further characterize the spectrum of clinical and genetic findings in HLRCC and to analyze characteristics that may be relevant to patient outcomes in this population.

Materials and methods

A retrospective chart review was conducted for patients with HLRCC evaluated at the University of Michigan between February 2007 and February 2020. Subjects were identified through query of the University of Michigan Cancer Genetic Clinic database and the institu-

Table 1. Patient characteristics

HLRCC patients (N)	57
Unique families	38
Sex, % (n)	
Female	71.9% (41)
Male	28.1% (16)
Age at diagnosis, mean (range) in years	
Overall cohort	44.4 (8-82)
Probands	45.2 (23-78)
Non-probands	43.1 (8-82)
Females	46.6 (8-82)
Males	38.8 (14-62)
Race, % (n)	
Caucasian	94.7% (54)
African American	3.5% (2)
Asian	1.8% (1)
Referral reason, % (n)	
Family history of HLRCC	36.8% (21)
CLM	49.1% (28)
CLM only	75% (21)
CLM and ULM	25% (7)
Cutaneous leiomyosarcoma and ULM	3.5% (2)
ULM and family history of cutaneous leiomyosarcoma	1.8% (1)
RCC	5.3% (3)

Abbreviations: CLM, cutaneous leiomyoma; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; RCC, renal cell carcinoma; ULM, uterine leiomyoma.

tional Electronic Medical Record (EMR, Epic). The study was approved by the University of Michigan Institutional Review Board (HUM-00167616). Subjects were included if they had a genetically confirmed diagnosis of HLRCC with a pathogenic or likely pathogenic germline variant in *FH* or clinical manifestations of HLRCC with confirmed family history of positive genetic testing for HLRCC. Patients with additional genetic variants were excluded.

Demographic data, referral reason, genetic diagnosis, HLRCC-specific phenotypic manifestations (CLMs, ULMs, and RCC), and data regarding other neoplasms were abstracted. If the EMR did not explicitly document presence or absence of CLMs, ULMs, or RCC, symptoms for each were queried via the EMR search function. The following search terms were used: pain, tender, cold, temperature, palpation, touch, blood, bleeding, dysmenorrhea, menorrhagia, dyspareunia, dysuria, and hematuria. The patient was deemed not to have these manifestations if the information remained unavailable after this search. In addition to histopathologic diagnoses, physicians' clinical diagnoses were included for CLMs. Imaging-confirmed diagnoses or symptom-driven uterine surgeries were used as a surrogate diagnosis for ULMs.

Results

A total of 61 patients with *FH* variants were identified. Fifty-five patients presented with HLRCC phenotype and *FH* pathogenic variant. Two patients presented with known familial *FH* pathogenic variant and personal HLRCC phenotype but had not undergone genetic testing. These 57 patients from 38 families served as the basis for our analysis. Three additional patients (including two from one family) with genetic variant c.1431_1433dup were excluded, as this is not considered pathogenic for HLRCC, but rather for hereditary *FH* deficiency and allelic recessive disorder. One of these patients had a clear cell RCC lacking any classic HLRCC-related pathological features; none had any HLRCC-specific manifestations. In addition, 1 patient with a germline *FH* pathogenic variant and a germline *RB1* pathogenic variant was excluded to limit analysis to patients that do not carry known pathogenic variants in other genes.

Patient characteristics

Demographic characteristics and reason for referral of the 57 patients with HLRCC are shown in **Table 1**. The majority identified as female (n=41, 71.9%) and White (n=54, 94.7%). The mean age at HLRCC diagnosis was 44.4 years (range 8-82 years). The most common reason for referral to cancer genetics was for evaluation of CLMs (n=28, 49.1%).

Cutaneous manifestations

Documentation of a full body skin examination was available for 56 patients. The overall prevalence of CLMs was 76.8% (n=43). Most patients recalled onset of CLMs in the 2nd to 4th decade of life. Histopathological confirmation was available for 33 of these patients. The mean age of biopsy confirmation of CLMs was 46.4 years (range 14-82).

Table 2. Characteristics of cutaneous manifestations of HLRCC (out of 56 patients who underwent full body skin examination)

Cutaneous lesions, % (n) and Mean age at time of biopsy in years (range)		
Typical Leiomyoma (CLM)	76.8% (43)	46.4 (14-82)
Leiomyosarcoma	5.4% (3)	49.0 (26-72)
Atypical leiomyoma	8.9% (5)	39.8 (25-56)
Distribution of CLM, % (n), out of 43		
Grouped	72.1% (31)	
Multiple regions	70% (30)	
Location of CLM, % (n), out of 43		
Trunk	55.8% (24)	
Scalp and neck	9.3% (4)	
Upper extremities	69.8% (30)	
Lower extremities	14% (6)	
Symptoms of CLM, % (n), out of 43	81.4% (35)	
Pain of any kind	58.1% (25)	
Intermittent pain	76% (19)	
Persistent pain	4% (1)	
Other pain	20% (5)	
Reported pain triggers	53.5% (23)	
Physical contact/pressure	34.8% (8)	
Cold/temperature changes	39.1% (9)	
Sunlight	8.7% (2)	
Stress	4.3% (1)	
Nocturnal pain	4.3% (1)	
Other/unspecified symptoms	9.3% (4)	

Abbreviations: CLM, cutaneous leiomyoma; HLRCC, hereditary leiomyomatosis and renal cell carcinoma.

CLMs typically presented as grouped lesions (n=31/43, 72.1%), most commonly on the upper extremities (including shoulders) (n= 30/43; 69.8%) but also on the trunk (n=24/43, 55.8%), lower extremities (n=6/43, 14%), and head/neck (n=4/43, 9.3%). Many patients had involvement of multiple locations (n=30/43, 70%) (**Table 2**). CLM sizes ranged from 0.2-2 cm, most commonly 0.5-1 cm, with rare lesions reaching 1.5-2 cm. All patients had multiple lesions. Symptoms were documented within CLMs in 35 (81.4%) patients; in the remainder, there was no mention of symptoms. Pain was most common, present in 25 cases (58.1%). Triggers for pain were documented in 53.5% (n=23) of patients with the most common trigger being exposure to cold temperatures or temperature changes (n=9/23, 39.1%) and physical contact or pressure (8/23, 34.8%).

Cutaneous leiomyosarcoma was diagnosed in 3 patients (5.4%), and atypical cutaneous leiomyoma (ALM) was diagnosed in 5 (8.9%). All patients with leiomyosarcoma or ALM had additional CLMs on examination. Mean age of diagnosis of leiomyosarcoma was 49 years (range 26-72), and ALM was 39.8 years (range 25-56). All were associated with pain. One leiomyosarcoma arose within a long-standing lesion with a 5-year history of slow growth. No reported changes occurred in the remainder. All 3 leiomyosarcomas were excised with 1 cm margins. No recurrence or metastases were observed by the time of data analysis (at 0.5, 2, and 10 years after diagnosis). Atypical features noted in ALMs were as follows: mild/focal nuclear pleomorphism (n=5; 100%), rare mitotic figures (n=4; 80%), and cytologic atypia (n=1; 20%). All 5 ALMs were excised with 0.5-1 cm margins.

Renal manifestations

Six out of 57 patients (10.5%) were diagnosed with RCC. **Table 3** illustrates the demographic and clinical characteristics for each of these 6

Table 3. Characteristics of renal manifestations of HLRCC

Sex	Age at RCC dx	Age at HLRCC dx	Genetic mutation	RCC Discovery	Symptoms	RCC Subtype	Furhman Grade	Metastasis	Death from RCC
F	28	29	c.697C>T	Symptomatic	Flank pain	Clear cell	3/4	No	No
M	30	31	c.698G>A	Symptomatic	Flank pain	Papillary Type 2	3/4	No	No
M	38	39	c.320A>C	Symptomatic	Weight loss, flank pain	Mixed; papillary and infiltrating acinar	4/4	Yes; local LNs, fat, renal vein	Yes; at age 39 yrs
F	50	51	c.1506dupA	Symptomatic	Flank pain	Papillary, unspecified	unknown	No	No
F	79	78	c.912_918del	HLRCC guideline-based imaging	n/a	Papillary Type 1	2/4	No	No
F	59	59	Deletion of entire coding sequence	Symptomatic	Flank pain	High grade RCC (per liver biopsy)	4/4	Yes; widely metastatic	Yes; at age 60 yrs

Abbreviations: Dx, diagnosis; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; RCC, renal cell carcinoma.

Table 4. Characteristics of uterine manifestations

Uterine lesions, % (n), out of 41 females	90.2% (37)
Preceding HLRCC diagnosis	97.3% (36)
After HLRCC diagnosis	2.7% (1)
Leiomyosarcoma	0% (0)
Atypical leiomyoma	7.3% (3)
Uterine procedures, % (n), out of 37 females with ULM	78.5% (29)
Myomectomy only	10.8% (4)
Global endometrial ablation (GEA) only	5.4% (2)
Hysterectomy, total	62.2% (23)
Hysterectomy s/p myomectomy	13.5% (5)
Hysterectomy s/p GEA	2.7% (1)
Symptoms, % (n), out of 37 females with ULM	45.9% (17)
Abdominal pain	21.6% (8)
Menorrhagia	18.9% (7)
Dysmenorrhea	16.2% (6)
Dyspareunia	8.1% (3)
Anemia	5.4% (2)
Nausea/vomiting	2.7% (1)

Abbreviations: GEA, global endometrial ablation; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; ULM, uterine leiomyoma.

patients. Four (66.7%) were female, and mean age of RCC diagnosis was 47.3 (range 28-79). Papillary RCC was the most common type (n=4, 66.7%). Four (66.7%) were diagnosed with RCC prior to HLRCC diagnosis, and two were diagnosed after. One RCC was diagnosed by surveillance for HLRCC-related kidney tumors. The second patient declined baseline imaging upon diagnosis but developed flank pain 9 months later, at which time imaging led to metastatic RCC diagnosis. CLMs were present in 3 of the 6 patients (50%; all female). Cutaneous lesions predated RCC diagnosis in all 3 by varying time periods (9 years, 30 years, and "long-term" per patient report). ULMs were noted in all 4 females with RCC. The two males with RCC did not have CLMs.

Uterine manifestations

Of 41 female patients, 37 (90.2%) had ULMs (**Table 4**). We observed no uterine leiomyosarcoma in our cohort. Most patients reported ULM onset in the 2nd to 3rd decade, with mean age of onset 30.5 years (range 20-40) among the 26 cases where age of onset was explicitly recorded. Mean timing of surgical or imaging confirmation of ULMs was 16.7 years prior to HLRCC diagnosis (range =1 month to 49 years). The most common symptom was abdominal pain (n=8/37). Uterine procedures were performed in 29/37 (78.4%) of females with uterine disease, most commonly hysterectomy (n=23/37). The mean age of hysterectomy was 35.2 (28-42) years. Histopathology from 7 patients was reviewed at our institution, unrelated to HLRCC evaluation, and 3 demonstrated atypical features, 1 of which prompted reflex *FH* testing leading to HLRCC diagnosis.

Other neoplasms

Two patients had a history of thin invasive melanoma prior to HLRCC diagnosis. Both melanomas were excised with appropriate margins. There were no metastases or recurrence at time of data analysis (at 7 and 21 years after diagnosis). Six patients had additional neoplasms that preceded HLRCC diagnosis, 4 of which were malignant (cervical cancer (2), ovarian cancer (1), and metastatic adrenocortical carcinoma (1)). The 2 benign neoplasms included a paraganglioma resected during RCC

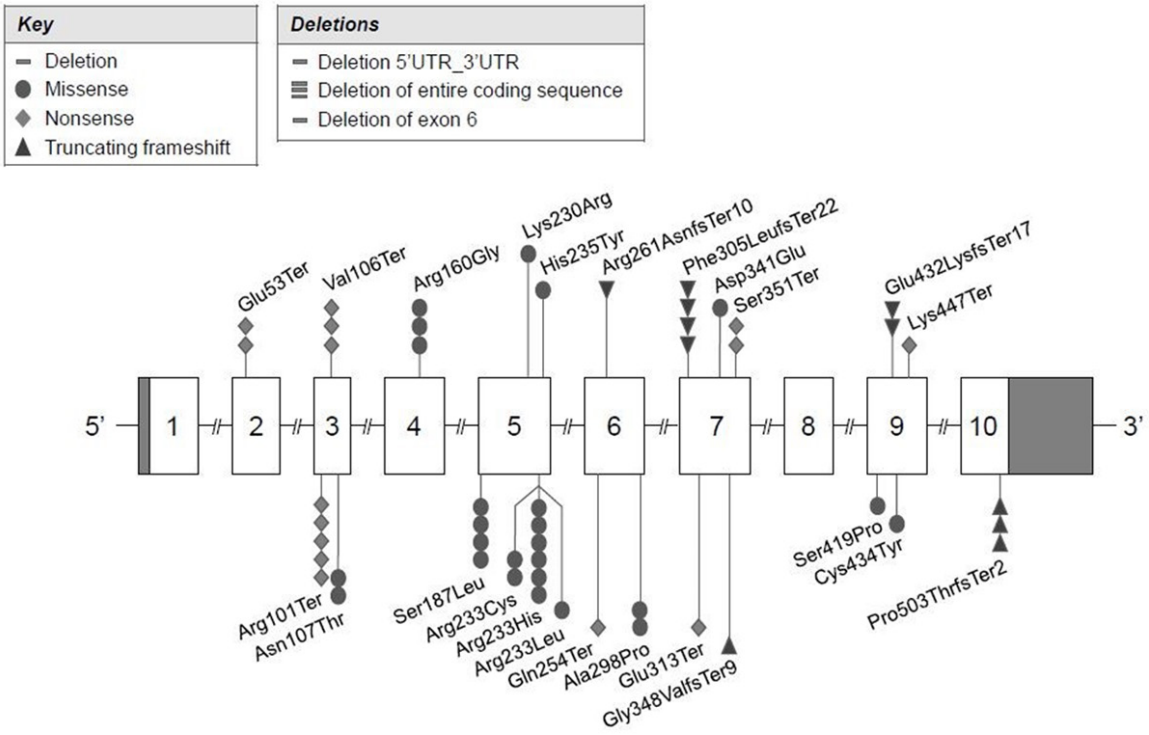

Figure 1. A lollipop plot illustrating the FH variants in the cohort of patients with Hereditary leiomyomatosis and renal cell cancer. There are 27 unique variants across 57 patients. At a given locus, the number of points represents the number of individuals with the unique variant. Missense variants are depicted by a circle (12 variants across 25 patients), nonsense variants are depicted by a lozenge (7 variants across 15 patients), truncating frameshift variants are depicted by a triangle (5 variants across 11 patients), and deletions are depicted by a bar (3 deletions across 5 patients). Deletions are listed in the top left corner of the figure. One patient had genetic testing per clinical documentation; however, a genetic test report was not available for review to determine the variant type.

resection and a pancreatic intraductal papillary mucinous neoplasm.

Genetic variants

A total of 27 unique variants in the *FH* gene were found in the present cohort (**Figure 1**; Supplementary Table 1). Per classification of CLIA-certified laboratories (Children's Hospital of Philadelphia, Invitae, Ambry, GeneDx) there were 23 variants classified as "pathogenic" and 4 variants classified as "likely pathogenic". These included missense variants, nonsense variants, truncating frameshift variants, an exon deletion, and deletions of the entire coding sequence. Location of variants spanned across eight exons of the *FH* gene (exons 2, 3, 4, 5, 6, 7, 9, 10).

Discussion

This retrospective study of 57 HLRCC patients from 38 families from a large tertiary referral center confirms key features of HLRCC [7-13] and expands the current understanding of the cutaneous, uterine, and renal manifestations that may be relevant to outcomes in patients with HLRCC. In particular, we highlight the crucial role of complete dermatologic examination for earlier diagnosis of HLRCC and associated RCC.

Studies have reported a wide range of estimates in lifetime risk of CLMs among HLRCC patients from 46% to 100% [7, 8, 10, 14, 15]. Our study included 56 patients who underwent a complete dermatologic examination and confirmed a high incidence of CLMs (76.8%), including in patients whose skin exams did not precede referral for genetic evaluation. CLMs presented as multiple grouped tender lesions most commonly on the extremities, but also on the head and neck and trunk, suggesting the importance of a full body skin examination in patients with suspected HLRCC. Pain associat-

ed with contact/pressure occurred as frequently as the historically "classic" descriptor of pain to cold temperature. Interestingly, symptoms were not documented in a number of patients, which may suggest some are symptom-free. Careful skin examination by a dermatologist may be necessary to detect some CLMs.

Cutaneous leiomyosarcoma and ALMs are also reported in HLRCC. In the current cohort, we found cutaneous leiomyosarcomas and ALMs in 5.4% and 8.9% of patients, respectively, which is slightly higher than the prevalence reported in previous studies [7, 8, 10, 16-20]. This suggests that routine dermatologic evaluation is valuable in patients with HLRCC to monitor for new or changing cutaneous lesions. Excision appears to be an effective treatment of leiomyosarcoma to prevent recurrence or metastatic disease.

Melanoma is not a core feature of HLRCC, but melanoma in situ (MIS) has been reported in at least 2 HLRCC cases outside of our study [21]. Our cohort included invasive melanomas in two patients. Further epidemiological and molecular studies are required to determine the relationship between melanoma and HLRCC.

According to previous studies, the incidence of RCC, including most commonly papillary but occasionally other histological subtypes, ranges from 10-20% and often predates the diagnosis of HLRCC [2, 19, 20, 22, 23]. Consistent with this, in the current cohort, 10.5% of patients had RCC, mostly papillary RCC (66.7%). Prior studies have not demonstrated a definitive relationship between CLMs and RCC incidence in the context of HLRCC [8, 9]. In our study, CLMs were present in 50% of patients with RCC, and the diagnosis of CLMs occurred prior to the diagnosis of RCC in all of these cases. This highlights the important role that dermatologists have in identifying CLMs, as this may lead to earlier diagnosis of HLRCC and associated RCC, which has potentially fatal outcomes if the diagnosis is delayed. Identification of papillary-type RCC often appropriately prompts genetics referral, thus it is commonly reported with HLRCC. Referral to genetics should be strongly considered in young patients with papillary and non-papillary RCC.

ULMs affect approximately 10% of females in the general population [24]. ULMs are exceedingly common in HLRCC (70-90%) [17, 25, 26] and the onset of ULMs in HLRCC is earlier than in the general population [27-29]. Our study found a similar prevalence of 90.2%. Most patients were diagnosed with ULM in their 20 s or 30 s. ULMs in HLRCC also often demonstrate loss of *FH* staining and positive cytoplasmic staining for S-(2-succino) cysteine [11]. Uterine leiomyosarcoma has been reported in HLRCC at a low frequency [2, 3, 8-10, 18-20], though most patients with uterine leiomyosarcoma do not have germline or somatic *FH* mutations [10, 30-32]. We did not observe any uterine leiomyosarcomas in the current study. Although ULMs are common in the general population, factors that should prompt consideration of evaluation for HLRCC include numerous and large ULMs, a family history of ULMs, ULMs with absence of *FH* staining, atypical features, and/or early-onset disease [33].

Our study found other neoplasms in a minority of patients. Though rare, paragangliomas are believed to be part of the HLRCC-associated tumor spectrum [19, 20, 34]. Future studies are needed to better elucidate the risk of other tumors in the setting of HLRCC.

There are several limitations to our study. As in prior studies, most of our patients were identified through HLRCC-associated manifestations, likely increasing the apparent incidence of CLM, cutaneous leiomyosarcoma, ALM, and RCC. A recent study utilizing *FH* germline data from large genomic databases found a higher incidence of *FH* alterations in the general population than previously thought, suggesting that penetrance of both CLM and RCC in HLRCC is significantly lower than reported in prior studies [35]. However, this approach might not accurately illustrate the prevalence of HLRCC and the associated risk for RCC. Future studies regarding the prevalence of HLRCC-related manifestations in non-probands are needed to decrease ascertainment bias. Other limitations of our study included lack of uniformity in patient and physician reporting and lack of consistent histopathology specimen availability. Finally, women are overrepresented in our cohort, which may be attributable to higher uptake of genetic testing and surveillance in this group [36-39]; in addition, women might be more likely referred as ULMs are only present in this group.

In summary, dermatologists play a key role in identifying patients with HLRCC. CLMs are the most common manifestation and often lead to a diagnosis of HLRCC; recognition of CLMs on physical exam is important to facilitate referral for genetic testing, which should be recommended in every patient with multiple CLMs. In addition, pathologists play a crucial role in highlighting atypical features in CLMs or ULMs, which further increase the suspicion for HLRCC. Early identification of patients with HLRCC allows for surveillance for RCC or leiomyosarcoma, potentially life-threatening manifestations. Genetic testing can also lead to family cascade testing to identify at-risk relatives who would benefit from pre-manifestation screening and early diagnosis of malignancies.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Variants in the *FH* gene found in the present cohort (N=27)

HGVS name[a]	*Amino acid change*	*Pathogenicity*[b]	*Variant type*
c.157G>T	Glu53Ter	Pathogenic	Nonsense
c.301C>T	Arg101Ter	Pathogenic	Nonsense
c.316del	Val106Ter	Pathogenic	Nonsense
c.320A>C	Asn107Thr	Pathogenic	Missense
c.478A>G	Arg160Gly	Pathogenic	Missense
c.560C>T	Ser187Leu	Likely pathogenic	Missense
c.689A>G	Lys230Arg	Pathogenic	Missense
c.697C>T	Arg233Cys	Pathogenic	Missense
c.698G>A	Arg233His	Pathogenic	Missense
c.698G>T	Arg233Leu	Pathogenic	Missense
c.703C>T	His235Tyr	Likely pathogenic	Missense
c.760C>T	Gln254Ter	Pathogenic	Nonsense
c.780_781del	Arg261AsnfsTer10	Pathogenic	Frameshift
c.892G>C	Ala298Pro	Likely pathogenic	Missense
c.912_918del	Phe305LeufsTer22	Pathogenic	Frameshift
c.937G>T	Glu313Ter	Pathogenic	Nonsense
c.1023T>G	Asp341Glu	Likely pathogenic	Missense
c.1041del	Gly348ValfsTer9	Pathogenic	Frameshift
c.1052C>A	Ser351Ter	Pathogenic	Nonsense
c.1255T>C	Ser419Pro	Pathogenic	Missense
c.1293del	Glu432LysfsTer17	Pathogenic	Frameshift
c.1301G>A	Cys434Tyr	Pathogenic	Missense
c.1339A>T	Lys447Ter	Pathogenic	Nonsense
c.1506dup	Pro503ThrfsTer2	Pathogenic	Frameshift
Deletion of exon 6		Pathogenic	Deletion
Deletion of entire coding sequence		Pathogenic	Deletion
5'UTR_3'UTRdel		Pathogenic	Deletion

[a]The reference transcript NM_000143.3 and NP_000134.2. [b]Per classification of CLIA-certified laboratories (Children's Hospital of Philadelphia, Invitae, Ambry, GeneDx). In cases where labs differed between "pathogenic" or "likely pathogenic", they were indicated as "pathogenic". Abbreviations: *FH*: *fumarate hydratase*; HGVS: Human Genome Variation Society.