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ORIGINAL ARTICLE

A retrospective review of 48 individuals, including 12 families, molecularly diagnosed with hereditary leiomyomatosis and renal cell cancer (HLRCC)

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Abstract

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is caused by autosomal dominant germline mutations in the fumarate hydratase (*FH*) gene and is characterized by cutaneous leiomyomas, uterine leiomyomas and aggressive renal malignancies. We conducted a retrospective chart review to characterize the patients referred to our Regional Genetics Program for assessment of HLRCC from 2004 to mid-2016. Forty-eight of 69 (69.5%) referred individuals were positive for a pathogenic or likely pathogenic variant in *FH;* they had an average age of 39.1 years. There were 11 different *FH* variants among them. As expected, the most sensitive indications for a positive genetic test were papillary renal cell carcinoma (RCC) at a young age (5/5; 100%) and multiple cutaneous leiomyomas (18/19; 95%). However, only twenty-two of 48 (46%) individuals with a positive molecular test had cutaneous leiomyomas, which is considerably lower than previously reported and supports the likelihood of ascertainment bias in previous reports. Notably, we have experience with 1 large family in which there were no cutaneous leiomyomas across a large age range. We confirm that multiple cutaneous leiomyomas and papillary RCCs at a young age have a high positive predictive value for a molecular diagnosis of HLRCC, but that cutaneous leiomyomas are less prevalent in HLRCC than previously understood, and therefore the condition is likely to be under-ascertained. Our understanding of the phenotypic spectrum of HLRCC is still evolving.

Keywords HLRCC · FH · RCC · Cutaneous leiomyomas

Abbreviations

FA	Fumaric aciduria
FH	Fumarase hydratase
HIF	Hypoxia inducible factor
HLRCC	Hereditary leiomyomatosis and renal cell cancer
NRF2	Nuclear erythroid 2-like 2 transcription factor
RCC	Renal cell carcinoma
2SC	S-(2-succinyl) cysteine

Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC, MIM 150800) is characterized by cutaneous leiomyomas, uterine leiomyomas and a predisposition to renal malignancies, typically an aggressive papillary type II renal cell carcinoma. HLRCC is caused by autosomal dominant germline mutations in the fumarate hydratase (*FH*) gene [1]. The enzyme fumarate hydratase catalyzes the conversion of fumarate to malate as part of the tricarboxylic acid cycle. Pathogenic variants in *FH* result in reduced enzyme activity by at least 50% [2], causing up-regulation of hypoxia-inducible factor (HIF) which may result in increased angiogenesis, glucose transport and growth stimulation. Fumarate may be an oncogenic metabolite as loss of fumarate hydratase has been shown to activate nuclear erythroid 2-like 2 transcription factor (NRF2), which may be involved in cancer development [3]. Fumarate also succinates cysteine to S-(2-succinyl) cysteine (2SC), and 2SC-modified proteins have been shown to be a reliable biomarker of *FH* pathogenic variants

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in uterine leiomyomas, RCCs [4] and cutaneous leiomyomas [5].

Germline pathogenic variants in *FH* are also implicated in other conditions: they predispose to malignant pheochromocytomas [6] and paragangliomas [6, 7] and they are also the cause of the autosomal recessive disorder fumaric aciduria (FA, MIM 606812) which is characterized by brain malformations, seizures, developmental delay and dysmorphic features.

Smit et al. proposed that the clinical diagnosis of HLRCC could rely on the single major criterion of multiple cutaneous leiomyomas, histopathologically confirmed, or the presence of at least 2 minor criteria which include severely symptomatic uterine leiomyomas requiring surgical treatment, type 2 papillary renal cell carcinoma before age 40 or a first degree family member with any of the above criteria [8]. Lehtonen et al. additionally suggested that collecting duct carcinomas be included in the criteria [9].

A definitive diagnosis of HLRCC is made with detection of a pathogenic *FH* mutation. The rate of positive genetic testing in individuals who meet the clinical criteria proposed by Smit et al. [8] is between 89 and 100% [8, 10]. The rate of positive testing when any of the major or minor clinical criteria is present has been shown to be 71% [2].

The prevalence of HLRCC has not been determined. Over 300 families with clinical findings of HLRCC and heterozygous mutations in the *FH* gene have been reported [2, 8, 11, 12]. The larger HLRCC characterization studies have relied on the presence of multiple cutaneous leiomyomas as a criterion for HLRCC testing [10, 13], thereby risking under-ascertainment of affected individuals.

Cutaneous leiomyomas have been reported in 76–100% of patients with HLRCC [8, 13]. The mean age of onset of cutaneous leiomyomas in the context of HLRCC is 25 years [10, 14], and 60–100% of *FH* germline mutation carriers over the age of 40 are reported to have cutaneous leiomyomas [8, 13]. The literature suggests that uterine leiomyomas are the most frequent finding in women with HLRCC, with greater than 80% having uterine leiomyomas by early adulthood [8] and up to 98% presenting with uterine leiomyomas at a mean age of 28–30 years [10, 15]. Renal tumors in HLRCC are typically of type 2 papillary histology and due to their aggressive nature are recognized as a distinct renal tumour subtype called HLRCC-associated RCC [16]. Collecting duct and clear cell cancers have also been reported in individuals with HLRCC [17]. Renal tumours in HLRCC are most often solitary and unilateral [18]. Estimates of a lifetime risk of renal cancer development in HLRCC vary widely and are approximated at 15% [19]. The mean age of RCC diagnosis in HLRCC has been reported as 41–43 years [2, 19, 20] however 4–7% of reported HLRCC cases have been in individuals below 20 years of age [19]. Genetic anticipation of RCC may occur in HLRCC [12]. Current recommendations are to consider genetic testing from the age of 8–10 years onward, and for individuals with positive genetic testing or a suspected clinical diagnosis to have an annual abdominal MRI [19]. There is no known genotype-phenotype association in HLRCC.

We believe that HLRCC is an under-reported cancer predisposition syndrome due to ascertainment bias for patients presenting with cutaneous leiomyomas. Here we describe our experience with patients referred to the Regional Genetics Program at the Children's Hospital of Eastern Ontario for HLRCC from 2004 to mid-2016 and compare our experience with that described in the literature.

Methods

Seventy-one individuals were seen for assessment of HLRCC at the Regional Genetics Program in Ottawa, Ontario, Canada from 2004 to mid-2016. All were seen by a geneticist, genetic counsellor or both for a clinical assessment that included a review of medical and family history and examination of any skin lesions. Individuals were offered molecular genetic testing for HLRCC if they had more than one cutaneous leiomyoma, a positive family history of HLRCC or a personal history of renal cell carcinoma before the age of 40. Genetic testing, performed at clinical laboratories in Canada or the United States, consisted of sequence analysis of the *FH* gene (single gene testing), and if negative, duplication/deletion analysis. In some circumstances, individuals were offered genetic testing even if they did not meet the proposed HLRCC clinical guidelines; this included an individual seen for a presentation of papillary RCC at age 43, and 2 individuals seen for a single (biopsy proven) cutaneous leiomyoma.

We conducted a retrospective chart review for these 71 patients and extracted the following data: number of families (2 or more individuals that were related), age at first Genetics clinic appointment, sex, indication(s) for referral, specialty of referring provider, clinical history (biopsy proven cutaneous leiomyomas, self-reported uterine leiomyomas, self-reported hysterectomy, biopsy proven renal cell cancer), examination findings (suspected cutaneous leiomyomas), family history of renal cancer, whether genetic testing was performed and the results of genetic testing.

The 71 individuals included 2 healthy adult individuals referred with a family history of fumaric aciduria. Individuals referred to our cancer genetics program for an indication other than HLRCC, who were offered *FH* testing were excluded from this review. We included the following clinical laboratory terms as a positive molecular result: 'positive for mutation' (commonly seen in clinical laboratory reports prior to 2012), 'variant, likely disease causing', 'likely pathogenic' and 'pathogenic'. We evaluated the pathogenic and

likely pathogenic variants in *FH* for the in silico predicted effect of the pathogenic variant on the protein product using the software program Alamut.

Results

We saw 71 individuals for an assessment of HLRCC between 2004 and mid-2016. They ranged in age from 9 to 91 years (average 41.6 years). In the majority of cases, there was a single reason for referral; however in two instances the reason for referral was both biopsy-proven cutaneous leiomyomas and a self-reported history of uterine leiomyomas. The most common reason for referral was a family history of HLRCC or FA (41/71; 58%) and most of these referrals were from primary care providers. The second most common reason for referral was biopsy proven cutaneous leiomyoma(s) (22/71; 31%), with most of these referrals from dermatologists. Five individuals were referred to us for presentation of a renal cell carcinoma by an oncologist; 4 of these presentations were symptomatic, and the other was revealed on imaging indicated for vesicoureteral reflux.

Sixty-nine of the 71 individuals decided to pursue molecular *FH* testing following genetic counselling. Two individuals declined molecular *FH* testing, with both citing insurance discrimination concerns. Forty-eight of the 69 tested individuals (70%) had a heterozygous pathogenic or likely pathogenic variant in *FH* (29 female and 17 male). Of the individuals who had a positive molecular result for HLRCC, 22/48 (46%) had cutaneous leiomyomas (19 biopsy-proven and 3 suspected on clinical examination). Of the 29 females with a positive molecular test result, 18 (62%) self-reported uterine leiomyomas; they ranged in age from 24 to 63 years at the time of their visit to the Genetics clinic. Five of 48 individuals with a positive molecular test result had renal cell carcinomas (Table 1).

Twenty-one of the 22 individuals referred with biopsy proven cutaneous leiomyoma(s) decided to pursue *FH* molecular testing; of these, 18/21 (86%) had a positive pathogenic or likely pathogenic *FH* variant. Of the 3 individuals who did not have a positive result, 2 had only a single cutaneous leiomyoma. Therefore 18 of 19 individuals (95%) with multiple cutaneous leiomyomas had a positive molecular test. The other individual who did not have a positive molecular result was a 44 year old female with a history of multiple cutaneous leiomyomas, 1 of which was biopsy proven, as well as self-reported multiple uterine leiomyomas and a family history of RCC. Sequencing and deletion/duplication analysis of this individual's *FH* gene did not reveal a pathogenic or likely pathogenic variant.

The five individuals referred with a presentation of RCC were positive for a pathogenic or likely pathogenic variant in *FH* (Table 2). The ages of these individuals at the time of RCC presentation ranged from 15 to 43 years. The RCC tumour histologies were papillary type II (3/5), tubulopapillary and papillary with sarcomatoid features. None of these individuals had cutaneous leiomyomas at the time of their RCC presentation. Two of the 3 females that presented with RCC (at the ages of 24 and 43) self-reported a history of uterine leiomyomas. In 4 of these 5 individuals, the predicted effect of the *FH* pathogenic or likely pathogenic variant was a premature stop codon.

Twenty-five of the 29 females with a positive genetic test result were over the age of 20; the remaining 4 were ages 9, 10, 14 and 15. Of the 25 females over the age of 20 who tested positive, 18 (72%) self-reported a history of uterine

Table 1 Characteristics of the population positive for an *FH* pathogenic or likely pathogenic variant

Total number of patients	48
Familial cases	9
Male	19
Female	29
Age[a]	
Average	39.1
Range	9–91
Reason for referral	
Family history HLRCC	24/48
Family history FA	1/48
Cutaneous leiomyomas	18/48
Uterine leiomyomas	2/29 women
Renal cell carcinoma	5/48
Referring provider	
Primary care provider	25/48
Dermatologist	16/48
Urologist/oncologist	5/48
Geneticist/metabolic specialist	2/48
Clinical features	
Renal cell carcinoma	5/48
Uterine leiomyomas (self-reported)	18/29 women
Average age[a]	45.4
Age range[a]	24–63
Hysterectomy (self-reported)	10/29 women
Average age[a]	55.3
Age range[a]	37–76
Hysterectomy and uterine leiomyoma (self-reported)	8/29 women
Cutaneous leiomyomas	22/48
Biopsy proven	19
Male	5/22
Average age[a]	53.8
Age range[a]	25–91
Female	17/22
Average age[a]	45.8
Age range[a]	32–76

[a]The age here is age when the individual was first seen in Genetics

Table 2 Characteristics of the population that presented with RCC

Age	Sex	Tumour histology	*FH* molecular test result[a]		Predicted effect of pathogenic variant	Diagnostic lab interpretation (year reported)	ClinVAR status December 2017
			Gene	Protein			
15	F	Tubulo-papillary	c.1430_1437dup	p.(Ser480Lysfs*6)	Stop codon at 485	Mutation (2008)	Pathogenic
24	F	Papillary with sarcomatoid features	c.797dupT	p.(Met266Ilefs*6)	Stop codon at 271	Mutation (2012)	Pathogenic
38	M	Papillary type II	c.965T > G	p.(Val322Gly)	Missense changing Val to Gly at 322	Variant, likely disease causing (2015)	Uncertain Significance
39	F	Papillary type II	c.1111A > T	p.(Lys371*)	Stop codon at 371	Mutation (2012)	Not listed
43	M	Papillary type II	c.1293delA	p.(Glu432Lysfs*17)	Stop codon at 448	Pathogenic variant (2016)	Pathogenic

[a]All variants were reported as heterozygous

leiomyomas. The remaining seven test positive females who did not have a known history of uterine leiomyomas ranged in age from 26 to 76 years (average 42.3 years).

Forty of 41 individuals referred because of a family history of HLRCC pursued *FH* testing, with 24/40 (60%) receiving a positive result of a pathogenic or likely pathogenic variant. One of the 24 individuals with a positive molecular test had a biopsy-proven cutaneous leiomyoma, and 3 of the 24 individuals had a skin lesion consistent with a cutaneous leiomyoma on examination in the Genetics clinic. The other 20 individuals with a positive *FH* molecular result did not have a history or clinical findings consistent with cutaneous leiomyomas. They ranged in age from 9 to 61 years (average 32.0 years).

The 71 referred individuals included 12 families, defined as at least 2 individuals reported to be biologically related. Families were assigned a single pedigree number. One of these families consisted of 18 individuals of African-Haitian descent: a 24 year old female proband who presented with a papillary RCC and uterine leiomyomas, and 17 first, second and third degree relatives referred because of this family history. The family members reported at least 3 other relatives with RCCs who were diagnosed elsewhere and not seen at our centre. Eleven of these 18 individuals tested positive for the pathogenic variant: 4 female and 7 male. Three of the 4 positive females had a self-reported history of uterine leiomyoma(s) (ages 24, 50 and 58 years old); the remaining female did not self-report uterine leiomyomas at 26 years of age. It is notable that none of the 11 individuals in this family who tested positive had a history of, or clinical findings consistent with, cutaneous leiomyomas. They ranged in age from 9 to 58 years (average 32.6 years).

The 48 individuals who were positive for a pathogenic or likely pathogenic variant in *FH* had a total of 11 unique variants (Tables 2, 3). Two of these variants, c.1103T > C and c.1111A > T, are novel *FH* pathogenic variants and are not listed in ClinVar or the *FH* Leiden Open Variation Database, and the other 9 variants have been previously reported

Table 3 Unique *FH* pathogenic or likely pathogenic variants in individuals presenting without RCC

FH molecular test result[a]		Predicted effect of pathogenic variant	Number of affected individuals	Number of unique pedigrees[b]
Gene	Protein			
c.688A > G	p.(Lys230Glu)	Missense	1	1
c.698G > T	p.(Arg233Leu)	Missense	1	1
c.706A > G	p.(Thr236Ala)	Missense	1	1
c.797dupT	p.(Met266Ilefs*6)	Stop codon at 271	11	1
c.1103T > C	p.(Met368Thr)	Missense	1	1
c.1104_1106delGCCinsACT	p.(Met368_Pro369delinsIleLeu)	In frame	4	1
c.1263delG	p.(Arg421Serfs*28)	Missense	1	1
c.1293delA	p.(Glu432Lysfs*17)	Stop codon at 448	16	12
c.1430_1437dup	p.(Ser480Lysfs*6)	Stop codon at 485	10	6

[a]All variants were reported as heterozygous

[b]The same pedigree number was assigned to all related individuals

in ClinVar as of December 2017. There was an overlap of 3 variants found in individuals presenting with RCC and those referred for other indications; all 3 of these *FH* variants (c.797dup, c.1293delA and c.1430_1437dup) had a predicted effect of an early stop codon, likely truncating the protein. These 3 variants accounted for 37/48 (77%) of the individuals with a pathogenic or likely pathogenic variant: 16 individuals with 12 different pedigree numbers had the c.1293delA variant; 11 individuals with 1 pedigree number had the c.797dup variant; and 10 individuals with 6 different pedigree numbers who all reported French-Canadian ancestry had the c.1430_1437dup variant.

Discussion

Our lower rate of positive genetic testing for HLRCC is likely attributable to the subset of individuals referred because of a positive family history, often with no HLRCC clinical findings, whereas other study populations have all had cutaneous leiomyomas. Our rate of positive genetic testing in individuals referred because of RCC or multiple cutaneous leiomyomata (96%, 23/24 individuals) is consistent with previously described rates in this cohort. The lack of a positive molecular result when HLRCC is strongly clinically suspected may be due to technological limitations, mosaicism, or other undiscovered genes or mechanisms being implicated in HLRCC. In cases where we have a high clinical suspicion for HLRCC and molecular testing is negative, we counsel individuals to undergo RCC screening. It could be helpful to perform 2SC immunohistochemistry studies in cases where clinical criteria for HLRCC is met and no *FH* pathogenic variant is found. Our positive test population had lower than previously described rates of cutaneous leiomyomas and also uterine leiomyomas. It is possible that some individuals may develop cutaneous leiomyomas or present with symptomatic uterine leiomyomas over time. However, it also appears that cutaneous leiomyomas may not be present in all affected families. Notably, the 11 members of the Haitian family positive for a familial pathogenic *FH* variant did not have any cutaneous leiomyomas. It is unknown whether the presence of cutaneous leiomyomas in HLRCC is influenced by ethnicity.

Limitations of our study include the retrospective review approach that relied partially on self-reported information and also that individuals were not followed over time. Long term studies with large cohorts will be essential to further characterize HLRCC; these studies are necessary to provide better estimates of the risk of RCC in HLRCC and to determine whether screening for RCC reduces morbidity or mortality. As well, it would have been of interest to perform biochemical studies to assess for fumarate hydratase enzyme activity level.

Our data confirm that multiple cutaneous leiomyomas have a high positive predictive value (18/19 individuals, 95%) for a molecular diagnosis of HLRCC. However, our data also demonstrated that cutaneous leiomyomas in HLRCC are likely to occur less frequently than previously thought, and may not be expressed at all in some families with a pathogenic *FH* variant. While dermatologists thus remain critical players in the identification of individuals with HLRCC and an important target group for educational initiatives about HLRCC, cascade testing of family members (via a referral to a geneticist or genetic counsellor) will remain critical to identify at-risk individuals. HLRCC is likely more prevalent than currently recognized due to the ascertainment bias of multiple cutaneous leiomyomas being the predominant recruitment factor in previous HLRCC studies. Our data also confirm that papillary RCC at a young age has a high positive predictive value for a molecular diagnosis of HLRCC, indicating that oncologists, urologists and possibly pathologists are another important target group for educational initiatives about HLRCC. The proposed guidelines suggest that individuals with RCC under the age of 40 be tested; however, we found a pathogenic variant in a 43 year old male presenting with a papillary RCC and we would advocate for referral at or below the age of 45.

We also report 2 pathogenic *FH* variants that are not listed in ClinVAR as of December 2017: one of these, c.1111A > T, was found in an individual that presented with an RCC, while the other variant, c.1103T > C was not associated with RCCs. We note that the c.797dupT variant was found in 11 members of a Haitian family of African descent with several individuals who had RCCs and uterine leiomyomas, and no individuals with cutaneous leiomyomas. This particular variant may not be associated with cutaneous leiomyomas or possibly cutaneous leiomyomas are less prevalent in individuals with HLRCC of African descent. Although there is no clear association between cutaneous leiomyomas in HLRCC and ethnicity, a previous description of 2 African-American families with HLRCC found either a single suspected or no cutaneous leiomyomas in affected individuals [21]. Our report of 6 French-Canadian families with the same pathogenic variant c.1430_1437dup may be consistent with a founder effect mutation. This variant was not seen in previous reports of French cohorts of HLRCC patients [2, 22]. We plan to perform haplotype analysis studies to identify possible founder effects for the c.1293delA and c.1430_1437 variants.

It has been well established that multiple cutaneous leiomyomas and papillary renal cell carcinomas have a high positive predictive value in molecular testing for HLRCC. However, the absence of multiple cutaneous leiomyomas clearly does not rule out the presence of a pathogenic *FH* variant, and follow up cascade testing of family members is necessary to diagnose HLRCC and ensure appropriate RCC

surveillance. Although not well estimated, HLRCC is likely more prevalent than previously understood. Educational initiatives about HLRCC should be targeted at oncologists and urologists in addition to dermatologists. Further long term studies of HLRCC are required to gain greater insights into the characteristics and clinical spectrum of HLRCC.

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