CHARACTERIZATION OF THE FUMARATE HYDRATASE (FH)

C.1431_1433DUPAAA VARIANT IN HEREDITARY

LEIOMYOMATOSIS AND RENAL

CELL CANCER SYNDROME:

A CASE SERIES

A Thesis Presented to the Faculty
of
California State University, Stanislaus

In Partial Fulfillment
of the Requirements for the Degree
of Master of Science in Genetic Counseling

By
Nanor Haladjian
May 2019
CERTIFICATION OF APPROVAL

CHARACTERIZATION OF THE FUMARATE HYDRATASE (FH) C.1431_1433DUPAAA VARIANT IN HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER SYNDROME:
A CASE SERIES

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Nanor Haladjian

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Date
DEDICATION

I would like to dedicate this research to my amazing family and friends who have provided me with constant support during the past two years of my graduate career. To my parents, Khoren and Silva, and my brother, Nareg – you are the driving forces behind any of my accomplishments. Thank you for your endless love and encouragement.
ACKNOWLEDGEMENTS

First and foremost, I would like to thank my committee members, Miya Frick and Niki Lovick, for not only introducing me to this topic, but for inspiring my interest in this field and providing me with guidance and support every step of the way. Thank you to Janey Youngblom for her insights, experience, and guidance throughout this project. I would also like to thank the UCSF Cancer Genetics and Prevention Program for working out the logistics to allow for this project to move forward.

I am immensely grateful for my classmates in the CSU Stanislaus Genetic Counseling Class of 2019 – I couldn’t imagine these past two years without your support and I can’t wait to see where the future takes all of us.
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ABSTRACT

Pathogenic variants in the fumarate hydratase (FH) gene are known to cause different diseases depending on whether one or both alleles carry the variant. Biallelic germline pathogenic variants in the fumarate hydratase FH gene are known to cause fumarate hydratase deficiency, a rare metabolic condition present in early childhood. Heterozygous pathogenic variants in the FH gene cause hereditary leiomyomatosis and renal cell carcinoma (HLRCC), where affected individuals present with smooth muscle tumors of the skin and uterus (leiomyomas), and have an increased risk of developing kidney cancer. The FH variant c.1431_1433dupAAA is known to result in fumarate hydratase deficiency in compound heterozygous form when in trans with another pathogenic variant. Historically, individuals identified to be heterozygous for this variant were assigned the diagnosis of HLRCC syndrome, however, the association of this variant with HLRCC has recently come into question. Medical literature is sparse when describing the association of this variant with HLRCC. This study describes the clinical phenotype and family histories pertaining to HLRCC of 22 patients identified to be heterozygous for the FH c.1431_1433dupAAA variant. No patients in this cohort had clinically documented or self-reported diagnosis of cutaneous leiomyomas. Uterine leiomyomas were diagnosed in 35% (7/20) of women in this cohort, at a mean age of 47.3 years. Only two women proceeded with hysterectomy due to the severity of fibroid-associated symptoms. No patients had a diagnosis of kidney cancer. The reported family histories were not consistent with HLRCC. This research suggests that the FH variant, c.1431_1433dupAAA, is not
associated with HLRCC in the heterozygous state, or may present as a low-penetrance allele.
CHAPTER I

INTRODUCTION

The fumarate hydratase (FH) gene encodes for the fumarate hydratase enzyme, or fumarase, which plays a significant role in the tricarboxylic acid (TCA) cycle. Homozygous & compound heterozygous germline pathogenic variants in the FH gene are known to cause fumarate hydratase deficiency, while heterozygous pathogenic variants lead to hereditary leiomyomatosis and renal cell carcinoma (HLRCC).

Fumarate hydratase (fumarase) deficiency is a rare, autosomal recessive, metabolic condition which is caused by the lack of properly functioning fumarase, leading to a disruption in the TCA cycle. Clinical presentation includes severe neonatal and early infantile encephalopathy, characterized by hypotonia, poor feeding, failure to thrive and seizures (Ewbank et al, 2006). Certain dysmorphic features, such as a depressed nasal bridge, frontal bossing, and widely spaced eyes, have been commonly seen with this condition, as well as notable microcephaly (Allegri et al, 2010). Affected children are typically nonverbal and non-ambulatory, and face poor outcomes in terms of disease progression – those who are severely affected often do not survive infancy, or may die during their first decade of life due to secondary complications (Loeffen et al, 2005). However, the clinical presentation and outcomes vary in severity, and some affected individuals present with a less severe course of disease and longer expected life span. Fumarate hydratase deficiency is suspected when there is an increase in fumaric acid in urine organic acid testing,
but the diagnosis is confirmed with either deficient fumarate enzyme activity levels, or the identification of homozygous/compound heterozygous pathogenic variants in the FH gene (Ewbank et al, 2006).

Heterozygous pathogenic variants in the FH gene lead to a separate, autosomal dominant condition, HLRCC, in which affected individuals present with benign tumors of smooth muscle tissue in the skin (cutaneous leiomyomas) and, in women, in the uterus (fibroids), and have an increased risk of developing kidney cancer (Pithukpakorn et al, 2006). Based on these findings, the FH gene has been classified as a tumor suppressor gene (Lehtonen, 2011).

Cutaneous leiomyomas are the most commonly seen feature of HLRCC, occurring in about 76%-100% of affected individuals, developing at a mean age of 25 years (ranging from 9-47 years), with most developing before the age of 40 (Stewart et al, 2006; Schmidt et al, 2014). It is reported that 73%-100% of women with an FH pathogenic variant are affected with uterine fibroids (Patel et al, 2017). Uterine fibroids in females with HLRCC are typically found to be larger in size, greater in number, and occur 10 years earlier than the typical diagnosis age in the general population. HLRCC-associated uterine leiomyomas have also been found to have characteristic morphologic features such as eosinophilic cytoplasmic inclusions, prominent eosinophilic nucleoli, and perinucleolar halos. Additionally, immunohistochemical staining positive for 2-succinocysteine (2SC) and loss of staining for FH can be seen in HLRCC-associated uterine leiomyomas (Joseph et al, 2015).
Renal cell carcinoma, typically solitary and unilateral type 2 papillary type, is a less common feature, with a lifetime risk around 15% for individuals with HLRCC (Menko et al., 2014). HLRCC-associated renal cell carcinoma tends to be more aggressive than sporadic renal cancer, and careful observation and intervention is warranted due to a high chance of metastasis, even for lower-stage tumors. HLRCC-associated renal cell cancer, like uterine leiomyomas, has also been shown to have characteristic morphologic characteristics such as large nucleus with prominent inclusion-like nucleolus and perinucleolar halo. Pathogenic germline FH variants in combination with a somatic “second-hit” cause the loss of fumarate hydratase enzymatic function, resulting in an accumulation of intracellular fumarate levels. The increased level of fumarate can spontaneously react with the cysteine sulfhydryl group of proteins, forming a stable chemical modification, 2-succino-cysteine (2SC). Therefore, HLRCC-associated tumors have been shown to present with positive 2SC and negative FH immunohistochemical staining (Chen et al., 2014). Additionally, HLRCC-associated renal tumors demonstrate a mixture of different growth patterns within the same tumor, such as tubulopapillary, cystic, and/or solid areas (Grubb et al., 2007; Skala et al, 2018). Diagnostic criteria for HLRCC, proposed by Smit et al, 2011, suggest a number of major and minor criteria for clinical diagnosis, as well as a definitive diagnosis via FH gene sequencing and detection of a positive germline pathogenic variant. (Table 1).
Diagnosis is likely when a patient meets the major criterion. HLRCC may be suspected if the patient meets ≥2 minor criteria. Occurrence of severely symptomatic uterine leiomyomas <40 years in second-degree paternal family members may also be relevant.

There is currently no formal consensus on clinical surveillance for individuals identified to have a single pathogenic FH variant. Provisional screening recommendations include full skin examination every one to two years to evaluate extent of cutaneous leiomyomas and annual gynecological exam to assess severity of uterine fibroids, provided by physicians familiar with the clinical manifestations of HLRCC. (Pithukpakorn et al., 2006.) Based on detailed literature review and a consensus meeting, suggested renal screening includes yearly MRI with 1-3 mm slices through the kidneys to detect for any small suspicious renal lesions followed by CT scanning to further characterize tumors. Prompt surgical management via open partial nephrectomy is recommended, even for smaller tumors (<3 cm) (Menko et al., 2014).

Table 1

<table>
<thead>
<tr>
<th><strong>Diagnostic Criteria for HLRCC</strong></th>
<th>(Smit et al, 2011)</th>
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<tr>
<td><strong>Major criterion</strong></td>
<td>Histopathologically confirmed multiple cutaneous leiomyomas.</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
<td>Surgical treatment for severely symptomatic uterine leiomyomas before age 40. Type 2 papillary or collecting duct renal cell carcinoma before age 40. A first-degree family member who meets one of the above-mentioned criteria²</td>
</tr>
<tr>
<td><strong>Definitive diagnosis</strong></td>
<td>Positive germline fumarate hydratase (FH) mutation test.</td>
</tr>
</tbody>
</table>

¹Diagnosis is likely when a patient meets the major criterion. HLRCC may be suspected if the patient meets ≥2 minor criteria.

²Occurrence of severely symptomatic uterine leiomyomas <40 years in second-degree paternal family members may also be relevant.
One FH pathogenic variant that has been identified is the c.1431_1433dupAAA (p.Lys477_As478insLys). Other nomenclature for this variant include p.K477dup, 435insK, 435insAAA, AAAins435, K434ins, c.1302insAAA, c.1433dupAAA, c.1433_1434dupAAA, c.1428_1429insAAA and c.1431insAAA. This variant is known to cause FH deficiency when paired with a second loss-of-function variant, and is the most frequently reported variant in individuals with FH deficiency. (Coughlin et al., 1998; Loeffen et al., 2005; Ewbank et al., 2006; Deschauer et al., 2006). The understanding of the FH gene’s association with HLRCC led to testing for clinical suspicion of HLRCC as well as the inclusion of FH on multi-gene hereditary cancer panels. Due to the known pathogenicity of the FH c.1431_1433dupAAA variant in FH deficiency, genetic testing companies historically reported this as a pathogenic variant associated with HLRCC. More recently, however, the association of FH c.1431_1433dupAAA with HLRCC has come into question, and among genetic testing laboratories the description of this variant has been revised several times, resulting in conflicting reports regarding its association with HLRCC at times. At least two major clinical laboratories in the United States that had originally classified this variant as pathogenic in HLRCC have now updated reporting to state that the c.1431_1433dupAAA variant is not associated with HLRCC. These classification updates are in part based on internal data gathered by the laboratories indicating that the variant has been identified in heterozygous form in a large number of individuals with no clinical presentation of HLRCC. However, there has not been a case series or published studies specifically to describe these
individuals. To date, there has been sparse literature describing clinical findings in relation to HLRCC in individuals found to be heterozygous for FH c.1431_1433dupAAA.

Ylisaukko-oja et al. (2006) screened 89 Polish patients with renal cell carcinoma, skin leiomyomas, or ovarian tumors for pathogenic FH germline variants, with the aim of examining the tumor spectrum associated with germline FH variants. Two out of the 33 patients from this cohort who were diagnosed with ovarian mucinous cystadenoma were identified to be carriers of FH variants; one with a novel variant and the other with the c.1431_1433dupAAA variant. The patient identified with the c.1431_1433dupAAA variant was diagnosed with the mucinous cystadenoma at age 49, and was also diagnosed with small uterine leiomyomas. She was evaluated by a dermatologist and underwent abdominal ultrasound, and no skin or kidney lesions were identified. This mutation was determined to be paternally inherited. The authors asserted that her father had no features associated with HLRCC, however, the specific evaluations completed to assess this were not described. Additionally, her family history included diagnoses of ovarian cancer in her FH pathogenic variant-negative mother. None of the individuals with skin leiomyomas or renal cell carcinoma were identified to have the c.1431_1433dupAAA variant.

Ezgu et al. (2013) described the case of a male diagnosed with fumarate hydratase deficiency, and upon FH gene sequencing, was found to have the c.1431_1433dupAAA pathogenic variant and a novel c.782G>T variant. His father
was heterozygous for the c.1431_1433dupAAA variant. His skin examination showed subcutaneous leiomyomas on his arms, though the number of leiomyomas were not specified nor pathologically confirmed. He also had a normal renal ultrasound.

In a study by Martinek et al. (2015), women who had a surgical intervention for a uterine leiomyoma before the age of 30 were identified in order to determine the presence of a pathogenic FH variant. Two patients with multiple leiomyomas and with confirmed germline FH pathogenic variants were identified, one of them being c.1431_1433dupAAA. The patient’s medical history included multiple hysteroscopic resections of submucous leiomyomas and laparotomy with subserous uterine leiomyoma enucleation between the ages of 23 and 26. The patient had a negative kidney ultrasound.

A case report by Pahl et al. (2018) describes a family with suspected Li-Fraumeni syndrome, brought to attention by a 14-year-old index patient with acute lymphoblastic leukemia (ALL), his mother with a diagnosis of cervical cancer, and other family members with various cancer types, not including renal cancer. The family history fulfilled Chompret criteria, and genetic testing was first ordered on the proband’s mother due to the index patient’s history of stem cell transplantation and limited germline DNA from fibroblasts. A multi-gene panel was done, which identified a pathogenic TP53 variant, confirming Li-Fraumeni syndrome, as well as the FH c.1431_1433dupAAA pathogenic variant. The FH variant was identified in the mother as well as her unaffected daughter, but not in the index patient in subsequent testing. The FH variant was considered an incidental finding, and the
authors mention the conflicting reports of pathogenicity available for this variant, though HLRCC cancer screening was recommended to the mother and her daughter. The mother underwent dermatology and gynecology screenings, and no HLRCC-associated findings were identified.

Preliminary data from a recent abstract presented at the 2017 American Association for Cancer Research annual Meeting by Walsh et al. (2017) queried 1375 individuals with cancer (no specified type), and identified the FH c.1431_1433dupAAA variant in 7 (0.5%) individuals with cancer. One patient with bladder cancer had a history of uterine leiomyomas, however, immunohistochemical staining for 2SC was negative. The other six carriers of the variant did not have any features of HLRCC. Additionally, this variant was not identified in any of the 178 patients in their study who had a diagnosis of kidney cancer. A full publication is pending, however, results of their findings suggest that this variant does not confer pathogenicity in the heterozygous form for HLRCC.

Various other cohort studies have been conducted looking at the relation between pathogenic FH variants and HLRCC phenotypes, however, the c.1431_1433dupAAA variant has not been found in these cohorts nor published in the literature. In a study by Gardie et al. (2011), 56 families were identified to have clinical features that were diagnostic or suggestive of HLRCC, namely, cutaneous leiomyomas. FH genotyping was done, and in 40 out of 56 of those families, 31 different FH sequence variants were identified – however the c.1431_1433dupAAA variant was not identified in any families. In another study by Smit et al. (2011), 33
families referred for HLRCC suspicion in the Netherlands were assessed for FH germline pathogenic variants, and in 14 families, 11 different pathogenic variants were identified, though not the c.1431_1433dupAAA variant. In similar studies, patient cohorts were ascertained due to features that aligned with a diagnosis of HLRCC – cutaneous leiomyomas, pathologically suggestive renal carcinoma, uterine fibroids as well as positive family histories. In these various cohort studies, FH sequencing was done and pathogenic variants were identified in 54 out of 98 patients (Lehtonen et al., 2006), 31 out of 35 families (Toro et al., 2003), and in 21 out of 21 families with HLRCC (Wei et al., 2006); the c.1431_1433dupAAA variant was not identified in any of these cohorts.

Further cohort studies are needed to understand the associated phenotype seen with this variant in relation to HLRCC, to inform on its clinical effects, and to guide screening and management recommendations for carriers. Despite the c.1431_1433dupAAA variant being a common variant in FH deficiency, it was not present in studies where individuals were ascertained based on HLRCC phenotype or family history. This suggests that the variant may not be associated with HLRCC.

To date, this study describes the largest cohort of patients (n=22) who have been identified as carriers of the c.1431_1433dupAAA FH pathogenic variant in order to further inform and characterize this variant as it pertains to hereditary leiomyomatosis and renal cell carcinoma.
CHAPTER II

METHODS

This research presents a series of patients identified to have the FH c.1431_1433dupAAA variant, and describes their clinical characteristics pertaining to HLRCC syndrome. The subjects in this case series are current or previous patients at the University of California, San Francisco (UCSF) Cancer Genetics and Prevention Program, where they had their genetic testing. Medical information was collected from patients’ electronic medical records and direct patient reporting, and information was summarized and grouped by clinical HLRCC findings.

Research Approval

The Internal Review Board (IRB) of California State University, Stanislaus, approved this research (protocol #1819-014, approved 9/28/18). This research is also approved under the University of California, San Francisco (UCSF) Cancer Genetics and Prevention Program long-term follow up and research IRB (protocol #10-04932). All patients included in this case series have been seen at UCSF and had previously consented to research participation.

Study Participants and Data Collection

Inclusion criteria for patients for the case series were: 1) over 18 years of age 2) had genetic testing through the UCSF Cancer Genetics and Prevention (CGPP) program which identified the FH c.1431_1433dupAAA variant and 3) consented to the UCSF CGPP long-term follow-up protocol. The UCSF CGPP maintains a database of all patients that have been seen for genetic counseling appointments,
including their genetic testing results, using the FileMaker Pro software, licensed specifically for use within the secure UCSF network. The FileMaker Pro database was queried specifically for individuals with the FH c.1431_1433dupAAA variant. The database search identified 27 patients with this pathogenic variant. Two of those patients had not consented to the UCSF CGPP long-term follow-up protocol, and upon review 3 patients deemed to have tested true-negative for the variant. The remaining 22 patients met inclusion criteria for the case study.

UCSF’s secure electronic medical records were accessed through the APEX system to collect retrospective clinical information on each patient. Information accessed included demographic information, genetic counseling notes, personal cancer history, dermatologic history, gynecologic history, surgical history, imaging reports, and pathology reports. Patient family history pedigrees were accessed using the Progeny web software licensed to the UCSF CGPP.

A letter informing patients about the nature of the study was mailed to the 22 qualifying patients. These patients were then contacted by telephone by the primary investigator to collect targeted and updated medical and family history information to supplement the information in the patients’ electronic medical records and pedigrees. Among the 22 queried patients, one had passed away, one specified that they did not want to be contacted by telephone for research, and three could not be reached after multiple attempts. As allowed by the UCSF protocol, the existing medical and family history information for these 5 patients was included in the study. The 17 patients that were successfully contacted via telephone provided updated information regarding
history of clinical skin exams, uterine fibroids, abdominal imaging, and family history, which was recorded in individual participant data sheets stored on the secure UCSF network. (See Figure 1).

Figure 1. Identification of study participants and data collection.
Data Analysis

General descriptive statistics were used to present patient characteristics and clinical findings.
CHAPTER III

RESULTS

Study Population

The study cohort consisted of 22 unrelated individuals, and the majority of study patients were female (20/22, 91%). The mean age of patients in the cohort was 48.6 with a range of 30 – 80 years. The distribution of patients within each 10-year age group is visualized in Figure 2. The ethnic ancestry was 95.5% Caucasian and 4.5% Hispanic, and 9 individuals (41%) reported Ashkenazi Jewish ancestry.

Figure 2. Number of patients in each age group.
The patients’ indication for referral for genetic counseling and testing varied: 12/22 (55%) were seen due to their personal diagnosis of cancer, 8/22 (36%) had no personal cancer history but were seen for their family history of cancers, and 2/22 (9%) had other clinical findings that prompted their referral. Of the patients who had a personal history of cancer, 9/12 (75%) had a history of breast cancer, four of which had a second cancer diagnosed as well. Table 2 provides the cancer history and ages of diagnosis for the individuals with a personal cancer history. Of the patients referred for other clinical findings, one (patient #18) had a finding of multifocal CHRPE (congenital hypertrophy of the retinal pigment epithelium). Another (patient #8) was referred for early-onset uterine fibroids with peri-nuclear halos identified on pathology, a morphological finding characteristic of HLRCC-related fibroids. Patient #8 was the only patient in the cohort who was referred to genetic counseling and had genetic testing specifically for a clinical suspicion of HLRCC.
Table 2

HLRCC-Associated Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Cutaneous Leiomyoma</th>
<th>Uterine Leiomyoma &amp; Age of Diagnosis</th>
<th>Cancer History &amp; Age of Diagnosis</th>
<th>Renal Cancer</th>
<th>Family History of Renal Cancer</th>
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<tr>
<td>1</td>
<td>55</td>
<td>F</td>
<td>No</td>
<td>Yes (42)</td>
<td>Breast (46); Papillary Thyroid (50)</td>
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<tr>
<td>2</td>
<td>43</td>
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<td>Breast (41); Basal and Squamous Cell (multiple, 20s-30s)</td>
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<td>3</td>
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<td>32</td>
<td>M</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>19*</td>
<td>58</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Breast (44)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>31</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>80</td>
<td>F</td>
<td>No</td>
<td>Yes (70)</td>
<td>Basal Cell (60); Lymphoma (79)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>22*</td>
<td>71</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>Papillary Thyroid (56); Urothelial (68); Basal Cell (69)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* = Clinical information collected from medical records only.

† = Age at death.
Among the type of genetic testing the patients received, 91% had a multi-gene panel through a clinical laboratory which included sequencing and deletion/duplication analysis. The germline genetic testing panels for these patients was from one of two clinical laboratories, Invitae or Ambry, and the size of the panels varied from 34 to 130 genes. One patient (#4) had paired germline and somatic tumor genetic testing through UCSF, which included 500 genes. Patient #8, who was referred for clinical suspicion of HLRCC, received single-gene FH sequencing & deletion/duplication analysis which identified the FH c.1431_1433 pathogenic variant, and later an expanded panel of genes due to her family history. Four out of the nine individuals of Ashkenazi Jewish ancestry (44%) were also identified to carry the APC risk allele (p. I1307K) commonly seen in Ashkenazi Jewish individuals, and 11 (50%) individuals in the cohort had one or more variants of uncertain significance (VUS) in various genes. No individuals were identified to have other pathogenic variants in any other genes other than what is described above.

All 22 patients in the cohort had the FH c. 1431_1433dupAAA variant identified on their testing. However, due to differences in the timing of testing, number of times this variant had been seen in other individuals, and uncertainty regarding this variant’s association with HLRCC, screening recommendations were not consistent between individuals. Of the 22 patients, 5 had originally been recommended to follow the provisional HLRCC screening recommendations, including yearly dermatologic exam, yearly gynecologic exam for females, and a baseline abdominal MRI followed by continued screening MRI every 1-2 years. Upon
further internal data gathered on this variant, review of HLRCC cohort studies and absence of the variant (Gardie et al., 2011; Smit et al., 2011; Lehtonen et al., 2006, Toro et al., 2003) and in consultation with the Cancer Genetics and Prevention Program’s clinical geneticist, the other 17 patients who were identified with this variant were not recommended to follow HLRCC screening guidelines. The five patients originally recommended to follow the guidelines were later re-contacted by a genetic counselor to inform them that the screening was no longer generally recommended. More personalized recommendations were given to patients based on their clinical and family histories; Patient #8, who had testing due to clinical suspicion of HLRCC, was recommended to continue her renal screening due to presence of severe fibroids with HLRCC-associated pathology features at an early age, as well as consideration of the patient’s preference for continual screening.

**Cutaneous Leiomyomas**

None of the patients in this cohort had a clinically documented or self-reported diagnosis of cutaneous leiomyomas. Fourteen individuals had documented or self-reported skin exams by a dermatologist or primary care provider (64%), none of which noted leiomyomas. Of these 14 individuals, 12 (86%) had skin exams documented in their medical charts, and 2 (14%) had self-reported information about their clinical skin exams. Three patients (Patients #7, 8, and 9) (14%) had dermatologic exams specifically for HLRCC screenings, and leiomyomas were not found on their exams. No patients self-reported any unusual, painful, or sensitive bumps.
Pedigrees were reviewed and individuals contacted in follow-up were questioned regarding any family history of cutaneous leiomyoma diagnosis, and none were reported.

**Uterine Fibroids**

Of the 20 females in this study cohort, 7 had a clinically documented or reported diagnosis of uterine fibroids (35%). The average age of uterine fibroid diagnosis was 47.3 years, ranging from 25 – 70 years. Table 3 lists these patients and their uterine fibroid history. Of these 7 patients, 2 had hysterectomies due to their symptomatic fibroids, at ages 46 and 47, respectively. Pathology notes available in the medical record for these 2 hysterectomies did not note morphological abnormalities, though evaluation for specific HLRCC-associated characteristics and immunohistochemical studies were not performed. Three patients had other forms of treatment for fibroids, including uterine ablation, embolization, and myomectomies. Patient #8 was diagnosed with symptomatic fibroids at age 25, underwent myomectomies, for which pathology identified prominent eosinophilic nuclei surrounded by a peri-nuclear halo – a pathological finding that raises the possibility of HLRCC. Of note, patient #8 also underwent resection for an abdominal mass adjacent to the ascending colon, which was diagnosed as a leiomyoma with degenerative features.
Pedigree analysis as well as direct patient reports identified that 3 patients from the cohort had a family history of uterine fibroids, though these cases did not prompt hysterectomy or further treatment. Two patients reported a family history of hysterectomy under the age of 40, and three with a family history of hysterectomy over the age of 40, though the reason for these hysterectomies was reported to be endometriosis.
Renal Screening

Among the 22 patients in this cohort, none had a diagnosis of renal cell cancer. Thirteen patients (59%) had undergone some type of radiological screening of their abdomen which included kidney imaging. Table 4 lists these individuals, their most recent imaging, the pertinent kidney results, and the indication for imaging. The average age of the patients at their most recent abdominal imaging was 53.8 years, with a range of 29 – 79.

Results of the renal imaging for 9/13 (69%) of the patients were noted to be completely normal, while 3/13 (23%) noted small cysts or hydronephrosis, both considered to be benign findings that did not warrant further evaluation. The CT results for patient #22 showed metastases of her urothelial cancer.

Patient #3 reported a family history of renal cancer in her paternal grandfather, who was diagnosed at the age of 89. No additional information regarding type of renal cancer, unilateral/bilateral, or pathology was known by the patient. It is unknown if the proband’s family member is a carrier of the variant. No other HLRCC-pertinent family history was present in patient #3’s pedigree. Pedigree analysis and patient reports for the other 21 patients did not reveal any other known history of renal cancer.
Table 4

Patients with Renal Imaging

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of Imaging</th>
<th>Age at Recent Imaging</th>
<th>Results of Imaging*</th>
<th>Indication for Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PET-CT</td>
<td>55</td>
<td>Normal</td>
<td>Breast cancer restaging</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>42</td>
<td>Normal</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>3</td>
<td>PET-CT</td>
<td>29</td>
<td>Normal</td>
<td>Breast cancer staging</td>
</tr>
<tr>
<td>4</td>
<td>CT</td>
<td>45</td>
<td>Normal</td>
<td>Ovarian cancer workup</td>
</tr>
<tr>
<td>5</td>
<td>US</td>
<td>64</td>
<td>Small cyst</td>
<td>Microscopic hematuria</td>
</tr>
<tr>
<td>6</td>
<td>CT</td>
<td>65</td>
<td>Normal</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>7</td>
<td>MRI</td>
<td>59</td>
<td>Small cyst</td>
<td>Pheochromocytoma workup</td>
</tr>
<tr>
<td>8</td>
<td>MRI</td>
<td>34</td>
<td>Normal</td>
<td>HLRCC screening</td>
</tr>
<tr>
<td>9</td>
<td>MRI</td>
<td>57</td>
<td>Normal</td>
<td>HLRCC screening</td>
</tr>
<tr>
<td>10</td>
<td>US</td>
<td>34</td>
<td>Normal</td>
<td>Nausea symptoms</td>
</tr>
<tr>
<td>16</td>
<td>PET-CT</td>
<td>68</td>
<td>Normal</td>
<td>Cancer workup</td>
</tr>
<tr>
<td>21</td>
<td>PET</td>
<td>79</td>
<td>Hydronephrosis, no malignancy</td>
<td>Cancer workup</td>
</tr>
<tr>
<td>22</td>
<td>CT</td>
<td>69</td>
<td>Metastases of urothelial cancer</td>
<td>Urothelial cancer restaging</td>
</tr>
</tbody>
</table>

* = Results of imaging specific to kidney findings.
Pedigree Tracking

Family history of cutaneous leiomyomas, uterine fibroids, and renal cell cancer was summarized, and patients who were contacted were also prompted regarding whether other family members had tested positive for this FH variant. Tracking of this variant in other family members was available for two of the patients in this cohort.

Patient #7’s mother also tested positive for the FH variant, and was not reported to have cutaneous leiomyomas, uterine leiomyomas, or renal cell cancer. She was 89 years old, and had a history of breast cancer at age 70 and bladder or vulvar cancer at 88.

Patient #21’s family (Figure 3) had identified a familial BRCA2 pathogenic variant in addition to this FH pathogenic variant. Patient #21, denoted as III-1 in the pedigree, only carried the FH variant, 2 of her sisters (III-6 and III-7) carried both the BRCA2 and FH variants, one other sister (III-8) carried only the FH variant, and her living brother and other sister were negative for both BRCA2 and FH variants. Her sister III-8 who carried only the FH variant did not have a history of cancer or any reported HLRCC features. Her sister III-6 had both BRCA2 and FH variants and a history of breast cancer, had a son (IV-10) who passed away at the age of 3 due to “congenital defects, a genetic disorder that was very apparent at birth,” reported by the proband. This sister’s daughter (IV-12) also tested positive for the FH variant, and was reported to be receiving regular renal screening. The patient’s second sister (III-7) with both the BRCA2 and FH variants had a personal history of ovarian
cancer, no other HLRCC features. No further information was known about testing status of other family members, and patient #21 denied any HLRCC features in any other family members.
Figure 3. Patient #21 pedigree.
This figure depicts the family history of patient #21, including reported cancers and FH variant status.
CHAPTER IV
DISCUSSION

The purpose of this study was to review the clinical characteristics of a cohort of patients who have been genetically tested and found to carry the FH c.1431_1433dupAAA variant. The clinical review focused on features that have been reported in the literature to be associated with this particular variant, which include hereditary leiomyomatosis and renal cell cancer (HLRCC). As recently as 2016, this variant was classified as pathogenic in the heterozygous state, and reports clearly stated that having this pathogenic variant was consistent with HLRCC syndrome. As the variant’s association with HLRCC has come into question in recent years, reports now state that its association is unclear. Based on the results of our current study, which includes the largest cohort of patients with the FH c.1431_1433dupAAA variant in the heterozygous state to date, the clear association between this variant and HLRCC is not supported in this particular patient population. This conclusion is based on the following factors.

Cutaneous leiomyomas are often the first manifestation of HLRCC, occurring in about 76-100% of affected individuals at an average age of onset of 25, with most patients developing them by 40 years of age (Patel et al., 2017). Cutaneous leiomyomas in HLRCC have also been documented to cause pain in greater than 90% affected individuals, either spontaneously or when induced by cold, touch, trauma, stress, or pressure (Alam et al., 2005). None of the patients in this cohort had a diagnosis of cutaneous leiomyomas, including the 14 patients who had clinical skin
exams done in the past, and all of the patients were older than the reported average age of leiomyoma diagnosis in individuals with HLRCC.

Uterine leiomyomas are also a highly penetrant feature of HLRCC, occurring in 73-100% of females with the syndrome, and are typically multiple, large in size, and typically have a mild to severe impact on patients’ quality of life. The age of onset and age of hysterectomy in individuals with HLRCC is typically 10 years earlier than diagnosis/treatment compared to the general population (30 years versus 40 years) (Patel et al., 2017) In our cohort, 7/20 women reported a diagnosis of uterine fibroids, and 5 women underwent treatment for them. This treatment involved hysterectomy for two women, myomectomies for one participant, as well as uterine ablation and uterine fibroid embolization for two others. The age of diagnosis and treatment in this cohort, however, is closer to the general population age of fibroid diagnosis, in a woman’s 40’s - 50’s. The high prevalence of uterine fibroids, at up to 70% of all women, further raises the question of whether the fibroids diagnosed in the women in this cohort are truly due to HLRCC syndrome, or if they are general population, sporadic fibroids (Stewart et al., 2017).

Studies have shown that HLRCC-associated uterine leiomyomas display certain morphologic features including alveolar-pattern edema, staghorn-shaped blood vessels, macro-nucleolus surrounded by a halo and cytoplasmic eosinophilic globules, as well as immunohistochemical stains showing up positive for 2-succinocysteine (2-SC) and loss of FH staining. However, the sensitivity and specificity of these features for predicting a FH germline mutation and HLRCC remains controversial (Joseph et
al., 2015; Rabban et al., 2019). Pathogenic variants in FH that are missense may still permit FH protein production, leading to normal FH immunohistochemical staining. Additionally, the antibody for 2-SC is not commercially available (Rabban et al., 2019). Patient #8’s presentation of symptomatic fibroids at the age of 25, with perinuclear halo identified in leiomyoma pathology, raised concern for HLRCC and triggered her referral for a formal genetic evaluation. The pathology of leiomyoma after hysterectomy for Patients #1 and #9 did not note abnormal nuclei, though more thorough pathological evaluation for HLRCC-associated morphology was not conducted as this is not current practice for unselected uterine leiomyoma. Patients #2 and #7 had treatment with ablation and embolization, with no uterine pathology. Patients #6 and #21 did not require treatment for their uterine fibroids, both of which were diagnosed well over the average age seen in HLRCC, which may be more suggestive of sporadic leiomyomas.

Renal cell carcinoma is the major malignancy reported in HLRCC, and is seen in around 15% of individuals with the syndrome with an average age of detection at 44 years. Renal tumors in patients with HLRCC have shown to be more aggressive than those in patients with other hereditary renal tumor syndromes, and often present with early metastasis despite small primary tumor size (Grubb et al., 2007). Renal cell carcinoma in HLRCC syndrome often presents with certain histologic features, like prominent nucleoli with perinucleolar halos and multiple architectural patterns within one tumor, though the morphologic presentation is broad (Skala et al., 2017).

Suggested HLRCC screening for renal cancer is still evolving – recommendations
from the 2013 HLRCC symposium suggest that individuals with a pathogenic variant should be monitored with yearly MRI with 1-3mm slices through the kidneys to detect very small tumors, as opposed to the more standard 4-5mm slice scan (Menko et al., 2014). Additionally, while active surveillance is the standard for small (<3cm) tumors to preserve renal function, this approach is not recommended for individuals with HLRCC due to the possibility of rapid metastases. Surgical management of even small renal tumors is suggested (Menko et al., 2014). The ideal age to begin screening also remains unclear. The symposium panel recommended predictive testing for a pathogenic FH variant from 8 to 10 years of age, with renal screening beginning thereafter, as there have been reported cases of renal cancer before age 20 in HLRCC (Alrashdi et al. 2010; Menko et al. 2014). This specific variant, however, has not been reported on its own in an individual with renal cell cancer. Similarly, none of the patients in this study cohort had renal cell cancer, and 55% of them were over the age of 44. Additionally, 59% of patients had abdominal imaging, either with an US, MRI, CT, or PET scan, and none had findings that warranted follow-up.

Patient #8 was the only patient in this cohort who was ascertained due to clinical suspicion of HLRCC. Her history of severe leiomyomas at ages 25 and 29, myomectomies, and HLRCC-associated leiomyoma pathology prompted her referral and resulted in the identification of this variant. It is unknown whether the FH variant was inherited maternally or paternally in her family. Family history pertinent to HLRCC features includes reported uterine fibroids in the patient’s mother in her 20’s, though she did not require treatment at the time. Additional cancer history in her
family include breast and uterine cancer in her mother, skin (unknown type) cancers in her brother at 34, father at 55, and maternal uncle at 40, and breast cancer in her paternal aunt in her 20’s. Patient #8 has had dermatology, gynecology, and renal screening, with normal skin and renal exams. Although regular HLRCC screening was no longer recommended for most patients in this study cohort, review of patient #8’s case and seemingly mild-HLRCC presentation, in conjunction with the patient’s preference to continue screening, prompted the recommendation for her to continue renal MRI screening, with reduced frequency to every 2-3 years in the absence of any findings or symptoms.

Medical literature currently available on FH pathogenic variants and HLRCC describe a highly penetrant tumor-predisposition syndrome, with clinical manifestation presenting with cutaneous leiomyomas, uterine leiomyomas, and in some cases, renal tumors. It is possible that previously reported incidence of the clinical features seen in HLRCC may be skewed due to ascertainment bias of those who are most severely affected, and the clinical picture of individuals with HLRCC may be much more variable. It is also important to note that in many of the larger cohort studies that have ascertained based on the typical HLRCC clinical features, the FH c. 1431_1433dupAAA variant has been absent (Gardie et al., 2011; Smit et al., 2011; Lehtonen et al., 2006; Wei et al., 2006; Toro et al., 2003).

The majority of patients in this cohort had genetic testing with a multi-gene panel, which included a number of genes associated with different hereditary cancer syndromes. The availability of Next Generation Sequencing (NGS) technology allows
for the sequencing of a larger number of genes simultaneously at a lower cost – which allows for detection of a wider variety of clinical indications. This also opens up the possibility of getting unexpected or incidental results. In this study cohort, 21/22 (95%) patients had genetic testing for indications other than suspicion for HLRCC. The FH c.1431_1433dupAAA variant was found incidentally by a multi-gene panel test, avoiding ascertainment bias towards individuals who may be the most severely affected. Currently, the ExAC population database reports an allele frequency of 0.0009071, or 0.09% for this variant. Though our sample size is small, results suggest that this variant may occur more frequently than previously understood in the general population.

Over the past 1-2 years, interpretations by major clinical genetic testing laboratories of this variant and its association with HLRCC have shifted. The most recent reports available from two major clinical laboratories now state that the FH c.1431_1433dupAAA variant is pathogenic in compound heterozygous state in association with FH deficiency, but not considered a risk factor for HLRCC in heterozygous state. The most recent report from Ambry Genetics (January 2019) notes that the variant has been detected in heterozygous state in a number of individuals internally, for whom no personal or family history suggestive of HLRCC was reported.

When this variant is identified incidentally on a multi-gene panel, as with this cohort, it can be a challenge to interpret associated risks and outline management and screening plans for unaffected carriers. Currently, the HLRCC symposium consensus
recommends predictive FH variant testing between 8-10 years of age, with renal MRI screening beginning yearly if a pathogenic variant is identified. While a more conservative renal screening may be suggested due to the aggressive nature of HLRCC-associated renal cell cancer, it is important to consider the drawbacks of additional screening, especially for a variant whose association with HLRCC is unclear. The specifically recommended annual MRI with 1-3 mm slices through the kidney can be more expensive and require higher field MRI scanners, and may or may not be covered by patients’ insurance coverage. The screening is more likely to identify incidental lesions, and recommendations for HLRCC suggest surgical management for even small (< 3cm) lesions, potentially leading to unnecessary and avoidable invasive procedures. The shift in the reporting and classification of this FH variant’s association with HLRCC will likely affect the clinical management of patients who had been identified as carriers in the past, as well as those who are identified with this variant in the future.
CHAPTER V
LIMITATIONS

There are several limitations in this study that may have affected the data. Firstly, data collection relied heavily on retrospective chart review, and not all information may have been available. Some information was verified directly by patients, but this method of data collection also relies on patient self-reporting. Patients did not all receive the same or standardized screening.

Not all patients had documented dermatology exams, and only a few had dermatology evaluations that specifically noted the absence of cutaneous leiomyomas based on the patient’s test result. It has been noted that cutaneous leiomyomas may go undiagnosed due to their generally benign nature and because they are a biopsy-proven diagnosis. Therefore, there is a small possibility that cutaneous leiomyomas exist in this cohort that were not recorded or self-reported.

Similarly, not all patients had imaging of their kidneys. Some methods of renal imaging that patients had, such as ultrasound, are not as sensitive as the recommended 1-3mm slice MRI. Family history information also relied heavily on patient reports and their knowledge of clinical presentation in family members. The FH variant was not able to be traced in the majority of the families included in the case series. Patient #3 was the only individual in the cohort who reported a family history of renal cancer in her paternal grandfather, however, his FH variant status is unknown. Finally, our sample size of 22 patients was small and included limited ethnic diversity.
CHAPTER VI

CONCLUSION

In conclusion, our study describes the clinical and family histories in relation to HLRCC syndrome in 22 patients who are carriers of the FH c.1431_1433dupAAA variant. The clinical data on this cohort of patients was not consistent with a classic HLRCC syndrome phenotype. Based on these findings, we propose the FH c.1431_1433dupAAA does not cause classic HLRCC syndrome in the heterozygous state, though there remains the possibility that it represents a low penetrance allele. Screening and management recommendations should be approached on an individualized basis, taking into consideration the patient’s personal and family history.
CHAPTER VII
FUTURE STUDIES

Next steps in clarifying the significance of this variant in its relation to HLRCC syndrome includes formal skin examinations for the individuals in this cohort, to definitively verify the presence or absence of cutaneous leiomyoma which is the most specific feature of HLRCC. Additionally, further pathological investigation of the uterine leiomyoma tissue blocks for patients #1 and #9 to check for FH-deficient and HLRCC morphology may provide additional information about the relation of their fibroids with HLRCC syndrome.

Additional studies involving larger cohorts of patients identified as carriers of the FH c.1431_1433dupAAA variant across different medical centers would be useful in continuing to describe the clinical phenotype of patients. A meta-analysis of all reported and published cases of this variant and its association with HLRCC, including these 22 patients, could provide useful information on the reported findings. A patient registry, documenting the variant and clinical manifestations, would also be beneficial in providing information and guidance for the management of patients who will be identified as carriers in the future. Prospective cohort studies following individuals identified with the FH c.1431_1433dupAAA variant over time to describe HLRCC-related clinical findings could provide helpful additional information. Possible prospective studies comparing individuals with this variant that undergo the recommended HLRCC screening with those who don’t to understand clinical
outcomes could be important to determine how to best care for individuals identified with this variant in the future.
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