

Case Report

Reed Syndrome in Eighteen Patients: A Genodermatosis Where Piloileiomyomas May Be the Diagnostic Clue

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Abstract: *Introduction:* Hereditary leiomyomatosis and renal cell cancer (HLRCC) is caused by germline heterozygous mutations of the fumarate hydratase (FH) gene. *Materials and Methods:* A retrospective observational study was conducted, aimed at characterizing the clinical features, histopathology, and genetic mutations in eighteen patients with confirmed HLRCC diagnosis. *Results:* FH gene mutations were identified in the seven families studied, including a previously undescribed mutation. All index cases of the families included were suspected on skin manifestations. Thirteen of the 18 patients (72%) presented cutaneous leiomyomas. The chief complaint was pain, with complete but transient response to botulinum toxin in one. No evidence of malignant transformation was observed. Uterine leiomyomas were present in seven of the eight women studied (88%). There was no evidence of renal cell carcinoma in any of the patients in the study. The most frequently found mutations were missense type (43%), followed by large rearrangements (24%), intronic deletions (14%) and nonsense (14%). A novel mutation not previously described in the literature is presented. *Conclusions:* HLRCC is a rare disease but it is also probably underdiagnosed. Dermatologists have an essential role in its diagnosis, by recognizing the clinical characteristics of the syndrome and investigating the family history.

Keywords: Piloileiomyoma, Genodermatosis, Reed Syndrome, Adnexal Tumor

1. Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is caused by germline heterozygous mutations of the fumarate hydratase (FH) gene. Thereby, the presence of multiple cutaneous and uterine leiomyomas and an increased risk of aggressive papillary type II renal cell carcinoma is typical. It is an autosomal dominant disorder caused by a germline mutation of the gene that encodes fumarate hydratase. The cutaneous piloileiomyoma different patterns and its association

with the gynecological and urologic features are here described. A variety of FH mutations may cause the syndrome, although the missense were the most frequent.

2. Main Manuscript

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC), also known as Reed syndrome, is a rare genodermatosis that predisposes individuals to multiple cutaneous leiomyomas, renal cell carcinomas, and, in women,

to uterine leiomyomas. Clinical features were first described in 1954 by Blum and Jeanl [1]. In 1973, after studying the members of two families and their successive generations, Reed *et al.* [2], described an autosomal dominant inheritance

pattern. Launonen *et al.* [3] established an association with type 2 papillary renal cancer [4, 5].

A series of major and minor diagnostic criteria have been established for diagnosing HLRCC, shown in Table 1 [4, 6, 7].

Table 1. HLRCC diagnostic criteria .

Main criteria:	
1.	Multiple cutaneous leiomyomas, especially with characteristic stabbing pain
2.	One or more piloileiomyomas with characteristic stabbing pain
Secondary criteria:	
1.	Solitary cutaneous leiomyoma and family history of HLRCC
2.	Type 2 papillary renal cell carcinoma before the age of 40
3.	In women, onset of symptomatic uterine leiomyomas before the age of 40.
4.	A first-degree relative who meets one of the above criteria. The presence of symptomatic severe uterine leiomyomas before the age of 40 in second-degree relatives on the paternal side may also be relevant.
Definitive diagnosis	
Positive for fumarate hydratase gene mutation	

The diagnosis is likely when a patient meets a main criterion.

The diagnosis may be suspected if they meet ≥ 2 secondary criteria.

HLRCC is caused by heterozygous mutations in the germline of the fumarate hydratase (FH) gene, defined as a tumor suppressor gene, located on chromosome 1 (1q42.3-43). The mutation in the FH gene has been identified in between 76 and 93% of the patients with clinical manifestations, although no correlation between genotype and phenotype has been identified [4, 8-12].

3. Patients and Methods

A descriptive observational cross-sectional study for data collection was performed. The analysis of the percentage of patients who develop kidney cancer during follow-up was performed with a longitudinal retrospective study. Information pertaining to patients who had been diagnosed with HLRCC with a positive molecular test, was collected.

The study included a total of 18 patients from seven families diagnosed between August 2011 and March 2019.

Once the project was approved by the Hospital Ethics Committee, we collected the data from the patients' medical records.

4. Results

The study was conducted on 18 patients from seven different families (families I to VII, named FI to VII), monitored from August 2011 until March 2019. Each family member was named with a consecutive Arabic index number (for example: FI-1), Definitive genetic diagnosis was achieved at an age ranging from 9 to 70 (mean age 45.1 years). The study participants included 10 men (56%) and 8 women (44%). The most common reason for a consultation was a family history. Eleven patients were referred for genetic consultation (11/18; 61%). Dermatology department flagged a suspected diagnosis in 7 of the 18 individuals in the study, (39%, see

Table 2).

Table 2. Characteristics of patients with study for positive FH gene mutation.

Total number of patients	18
Families	7
Women	8
Men	10
Age genetic diagnosis confirmed	
Average	45
Range	(9-70)
Reason for consultation	
Cutaneous leiomyomas	7
Uterine leiomyomas	0
Family history of HLRCC	11
Renal cell cancer	0
Service that flags the possible diagnosis	
Dermatology	7
Genetics	11
Gynaecology	0

A family history of HLRCC was observed in 15 of the 18 patients (83%). Of the remaining three, two had a suggestive family history: one (F V-1) described the presence of similar skin lesions in their father, while another patient (F VI-1) mentioned their sister had undergone surgery for uterine fibroids (negative genetic study) and their mother had died of renal cancer aged 36, in the absence of evidence of histological type.

4.1. Cutaneous Leiomyomas

Thirteen of the 18 individuals (72%) presented cutaneous leiomyomas, with an average presentation age in both sexes of 43, ranging between 16 and 70 years of age. In men, cutaneous leiomyomas (CLs) were observed in 7/13 (54%) with an average presentation age of 44, while in women these were found in 6/13 (46%), at an average age of 41.

Of the 13 individuals with CL, 12 had a skin biopsy. In the histopathological study, all of them were diagnosed with piloileiomyoma (Figure 1).

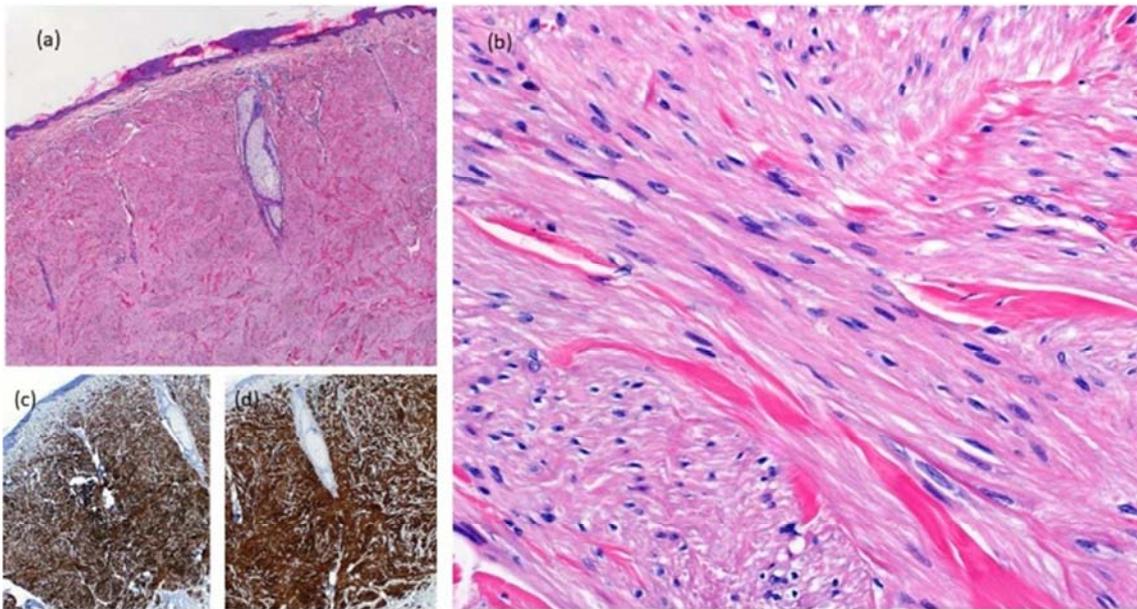


Figure 1. Histology: a) Hematoxylin-eosin stain 4x: circumscribed non encapsulated. b) Higher magnification (H-Eo 20x): bundles and fascicles of smooth muscle cells with eosinophilic cytoplasm and cigar-shaped nucleus. c) Actine 20x and d) Desmine 20x: intense positivity in immunochemistry.

Two CL distribution patterns were observed: a scattered pattern in 7 individuals (54%) and a mixed (grouped segmental lesions in association with scattered lesions) present in 6 of the 13 individuals (46%) (Figure 2). In most cases, patients reported an increase in the number and size of CLs. In the majority of the patients, the CLs were distributed across the trunk and upper limbs. Eight patients complaint of

symptoms (8/13; 61%): 6 reported pain and 2 pruritus. Botulinum toxin infiltration was tested in one patient that presented numerous and very painful CLs refractory to conventional analgesia in the dorsal area. A positive but transient response was achieved, as the patient's pain recurred 7 months after the treatment (Table 3).

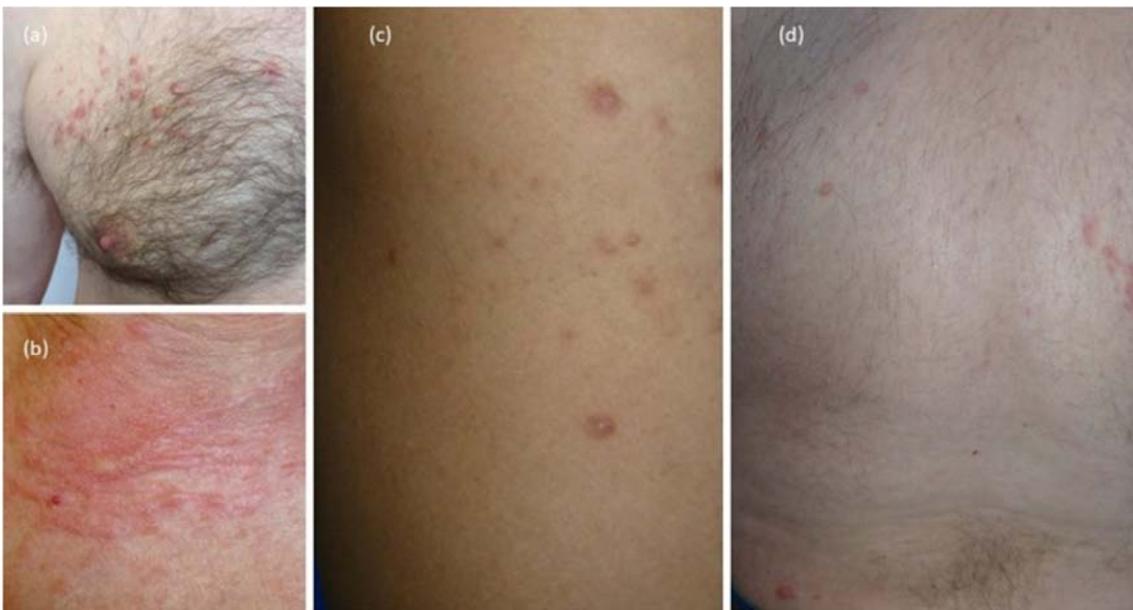


Figure 2. Cutaneous leiomyomas: a) papule-nodule grouped in the right pectoral; b) papules grouped in a plaque at the neckline; c) brownish papules scattered on the back; d) mixed pattern: scattered papules on the back coexisting with a segmental pattern affecting right scapula.

4.2. Uterine Leiomyomas

Seven of the eight women (88%) had uterine leiomyomas (UL), at an average age of 35 (range: 27-49 years). Three patients were symptomatic, two patients reported a history of

metrorrhagia, causing iron deficiency anemia in one (F II-3); in another, who reported puffiness, evidence of a giant uterine myoma was found in the gynecological study. Three patients (43%) (F I-1, F IV-1, F VI-1) had a hysterectomy at an average age of 34 (range: 33-34 years). One underwent a myomectomy

(F II-3) (Table 4).

Table 3. Characteristics of the cutaneous leiomyomas.

Total number of patients	18
Presence of cutaneous leiomyomas (CL)	13
Skin biopsy	12/13
CLs in men	
Presence of CLs	7/13
Average age of onset	44
CLs in women	
Presence of CLs	6/13
Average age of onset	41
Resulting anatomical pathology	
Piloileiomyomas	12/12
Distribution pattern	
Segmental and scattered	6/13
Scattered	7/13
Presence of symptoms	
Symptomatic	8/13
Pain	6/8
Pruritus	2/8

Table 4. Uterine leiomyoma characteristics.

Total number of women in the study	8
Uterine leiomyomas	7/8
Average age of onset	35
Age range	27-49
Hysterectomy	3/8
Average age	34
Age range	33-34
Myomectomy	1/8
Age	NA

4.3. Renal Cancer

In the retrospective study carried out, there was no evidence of renal tumors in any of the individuals, who underwent periodic annual magnetic resonance imaging.

However, in three patients, we identified a family history of renal cancer; two of these were siblings whose mother and maternal uncle both died from this cancer at the ages of 46 and 45, respectively (F III 1-2). Only the histology of the mother’s tumors, which turned out to be a papillary tumors, is known.

In the case of the other patient, the mother died of renal cancer at the age of 36, but the histology is unknown (F VI-1).

Concerning the other types of tumors, one individual developed a vesical neoplasm at the age of 57, two years after a confirmed diagnosis of HLRCC (F IV-2). Another patient had an image compatible with right adrenal adenoma on MRI (F VI-1).

Reviewing the MRI reports of the different patients to search for the appearance of a tumor mass, a high prevalence of renal cysts was found. These were present in 11 out of the 18 patients, in other words, 61%. Of these, 5 presented in a single kidney (45%), while the remaining 6 had bilateral cysts (55%).

4.4. FH Mutations

The study involved individuals who had FH gene mutations, so 100% had a positive confirmatory genetic study. Among the 18 individuals, there were seven mutations, different for each of the families, as shown in Figure 3 and Table 5. All mutations were detected in heterozygosity.

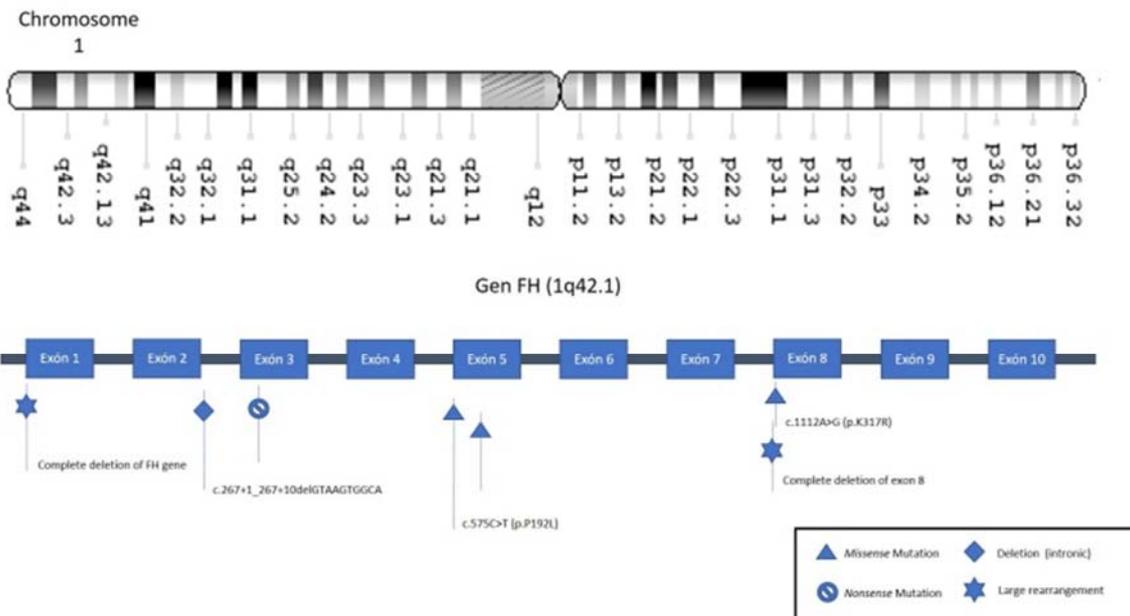


Figure 3. Schematic diagram of fumarate hydratase gen with mutation locations.

The following types of mutations were observed: missense in three families (43%, F I, IV and V), in a total of 11 individuals; nonsense in one family (14%; F VI), in one

individual; significant reordering in two families (29%; F II and III), in a total of five individuals; and intronic deletion in one family (14%; F VII), in one individual). All of the

above-mentioned mutations were classified as pathogenic.

One of the seven mutations (F V-1) is a previously undescribed variant, the c.1112A>G mutation. It was observed in a Peruvian 32 year-old man, whose clinical features were consistent with HLRCC. A reduced activity of the fumarate hydratase enzyme was demonstrated, (38 nmol/min/mg). This novel mutation was classified as type 4 variant (probably

pathogenic), although it should be considered a variant of unknown significance.

Interestingly, we have been able to observe that, in individuals of the same family who present the same mutation, the clinical expression can vary, with some presenting CLs while others do not.

Table 5. Characteristics of the mutations in this study.

Positive / Studied	Family	Mutation	Type	Pathogenicity (1-5) ¹²
I 5 / 6		c.575C>T (p.P192L)	Missense	Pathogenic (5)
II 4 / 6		Complete deletion of FH gene	Significant reordering	Pathogenic (5)
III 2 / 4		Exon deletion 8**	Significant reordering	Pathogenic (5)
IV 4 / 5		c.697C>T (p.R233C)	Missense	Pathogenic (5)
V 1 / 1		c.1112A>G (p.K317R)	Missense	Probably pathogenic (4)
VI 1 / 2		c.301C>T o p.R101*	Nonsense	Pathogenic (5)
VII 1 / 3		c.267+1_267+10 from GTAAGTGCCA	Deletion (intronic)	Pathogenic (5)

5. Discussion

The prevalence of hereditary leiomyomatosis and renal cell cancer (HLRCC) is unknown. Only 200 families have been reported so far, most of whom were documented in England, North America and Finland [6], although the incidence appears to be higher among descendants of Eastern European populations [4]. It is probably an underdiagnosed syndrome.

In our series, 39% of HLRCC cases were referred to the Genetics Department by the dermatologist, and 61% were diagnosed through a study undertaken by the Genetics Department itself. It seems therefore that the role of dermatologists is important when it comes to recognizing cutaneous leiomyomas and their possible implication in a syndrome such as HLRCC, as every index case of each family was detected by a dermatologist.

As far as the clinical expression of this syndrome is concerned, no differences have been noted between the sexes in previous reports. However, in our study, the onset of CL in women occurs earlier (41 years of age) than in men (average 44 years of age). Only a few published articles refer to the age of onset. Bholá et al [13], in a retrospective study, found that the average age CLs appear, is lower in women than in men (46 for women; 53 for men).

The prevalence of CLs in patients with the FH gene mutation was 72% in our series; which is in line with the high percentages recorded in other series, in which they reach 90% [4, 13].

Additionally, no differences in the prevalence of CLs according to the different sexes were observed. CLs are often the first manifestation, however, in our series, two patients were previously diagnosed with uterine leiomyomas, being diagnosed with UL at the ages of 34 and 49.

With regard to CL, no predominant pattern has been described, although, in the majority of case series, the three most-frequently described patterns were: segmental, scattered, and a mix of these two, as in our series [5, 14-16]. The proportion of symptomatic patients; reached 61% in our

series (8/13). One particularly symptomatic patient with intense pain that did not respond to conventional analgesia received intralesional botulinum toxin. In no patient of our series was there evidence of the malignant transformation of CLs to leiomyosarcomas, this being a rare manifestation, even though in the series of published cases this was evidenced in two people from different studies [5, 17]. Concerning the histological types of CL, all of the biopsied samples were consistent with piloleiomyoma.

The vast majority of female patients (88%) were diagnosed with UL, which was consistent with the published literature on HLRCC syndrome (73-100%) [4]. The average age for UL diagnosis was 35 years. Sixty-eight percent of the women with HLRCC, were given a hysterectomy before the age of 40 [11], ten years earlier than in the general population [4]. In our series there was no case of malignant transformation to leiomyosarcoma; this differs from the percentages of malignancy reported in other studies [14].

During the follow-up no patients developed renal cancer, so we were not able to analyze this association. However, we did find other tumors, such as a bladder cancer and an image compatible with right adrenal adenoma. These two findings are also mentioned in the literature consulted as possibly being associated with HLRCC syndrome, but more studies are required in order to be able to confirm this association [6, 7, 9, 19].

On the other hand, 61% of the patients presented renal cystic lesions in the annual radiological studies for the early detection of RCC. Various studies mention a higher prevalence of benign renal cysts in individuals affected by HLRCC evaluated to 42%. This represents a higher prevalence compared to the general population, which is around 10% [9]. Therefore, this finding may not be a very sensitive for diagnosing HLRCC.

In the series of Lehtonen et al. [19], eight families were studied: five individuals out of the 14 patients with who presented renal cystic lesions were diagnosed with RCC renal cell cancer (RCC), meanwhile the imaging tests for seven patients with RCC did not present lesions suggestive of cystic content. The relationship between cystic lesions and the

occurrence of RCC is, therefore, not entirely clear.

A correct estimation of the risk, using the Bosniak classification system of renal cystic masses, may help to establish different degrees of suspicions of malignancy, since, in initial stages, a renal neoplasm could resemble a RCC.

We identified seven different mutations of the FH gene in heterozygosis in all the individuals, a finding consistent with the autosomal dominant hereditary pattern of the disease.

The majority of the mutations are of the missense type, constituting 43% of the FH gene alterations found distributed by family, similar to other published series [11, 20, 21]. Of the total mutations observed, one has not previously been described in ClinVAR c.1112A>G (p.K317R). This mutation presented specifically in a Peruvian patient, diagnosed by the Dermatology department due to the presence of CLs on the upper limbs. These appeared at the age of 32, and were reported as piloileiomyomas by the Pathology department, showing reduced activity of the FH enzyme (38 nmol/min/mg prot), which was therefore interpreted as fumarase activity decreased with respect to the control range (62-173), compatible with the mutation-carrying character of the gene coding for fumarate hydratase.

Albeit the presence of RCC was not reported in our study, we highlight the mutation comprising the deletion of exon 8, which constitutes a significant reordering, present in two siblings mentioned above, who had a family history of renal carcinoma - their mother and maternal uncle died from this cancer at the ages of 46 and 45, respectively. Another patient carrying the nonsense mutation c.301C>T or p.R101*, pathogenic as it produces a truncated protein, has a family history involving the death of their mother from renal cancer, aged 36, with no known histology.

A couple of early studies suggested the existence of mutations with an increased RCC risk, currently the type of FH gene mutation does not appear to be an essential factor in the development of renal cancer, nor is there clear evidence of increased risk in patients with a previous family history of renal cancer [9, 18, 20, 21]. It is remarkable that the penetrance of this syndrome may be very variable.

Although association of uterine and cutaneous leiomyomas with RCC in Reed syndrome is not very high (20-34%) [4], it constitutes the main fact to monitor in patients with HLRCC. Annual screening with abdominal MRI since childhood should be performed. The youngest patient included in this series was a 9 years old child.

These renal neoplasms are very aggressive tumors, with an average diagnosis age of 43, and where approximately 2/3 present stage III/IV at diagnosis [6]. Given the aggressiveness of these tumors, the "3 cm rule", which allows a conservative attitude when the renal masses do not exceed this size, cannot be applied in hereditary leiomyomatosis related cases, since even solitary and primary tumors can metastasize [21, 22].

The main limitation of the study was the small number of patients (n=18), which prevented us from obtaining statistically significant results. Additionally, since this is a retrospective study, it is possible that there was bias in the collection and selection of the information.

6. Conclusion

HLRCC is a rare, infrequent disease, but it is very likely that it is underdiagnosed, as highlighted by other authors [16]. This may be due to a lack of knowledge about its cutaneous manifestations (CL) or its association with the presence of UL at young ages. For this reason, it is essential to recognize the clinical features of the syndrome and investigate the family history. In our series, 100% of index cases of the studied families were suspected on skin manifestations. A similar percentage to the referred in literature presented cutaneous leiomyomas (72%), although detected at a younger age. The presentation pattern varied in the same proportion, 54% were scattered pattern while 46% were grouped. As discussed previously, CL may be symptomatic and botulinum toxin may be a valid treatment.

Uterine leiomyomas would be present in almost 90% of women, most of whom were diagnosed in their middle thirties. More than a half would have a hysterectomy performed, on average, 10 years before general population. Attending to renal malignancies, none of the patients included in the studied developed renal cell cancer, although when developed, they tend to be aggressive tumors and annual screening with abdominal MRI since childhood is strongly recommended. A variety of gene mutations have been described, predominantly missense type. It is remarkable that the penetrance of this syndrome may be very variable. We present a novel mutation not previously described in the literature.

In conclusion, Reed syndrome is a heterogeneous syndrome that brings together a variety of manifestations. The prompt recognition of the syndrome would make possible to diagnose these patients and be able to monitor them with radiological controls to screen for renal cancer, allowing early diagnosis and treatment with the most conservative surgical technique possible. Therefore, the role of dermatologists is essential for the screening of suspicious cases.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this research article and any accompanying images. All the patients (or parent/legal guardian) have provided written consent to publish the details and photos of their case.

The study was approved by the Institutional Review Board of the Hospital Universitario Príncipe de Asturias (TFG/M 10/2019).

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors contributed equally in the manuscript elaboration.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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