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Lipoid proteinosis: Novel *ECM1* pathogenic variants and intrafamilial variability in four unrelated Arab families

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Abstract

Background/objectives: Lipoid proteinosis (LP) is a rare autosomal recessive multisystem disorder that is caused by loss-of-function pathogenic variants in the extracellular matrix protein-1 (*ECM1*) gene. The typical clinical manifestations of LP include hoarseness of voice, beaded papules on the eyelids, infiltration and scarring of the skin and mucosa, as well as neuropsychological abnormalities. Currently, more than 70 pathogenic variants have been reported, including nonsense, missense, splice site, deletion and insertion pathogenic variants, and more than half of them occurred in exons 6 and 7.

Methods: Clinical evaluation and Sanger sequencing were performed on eight patients from four unrelated Arab families.

Results: We identified two novel *ECM1* variants, one nonsense pathogenic variant in exon 6 (c.579G>A, p.Trp193*) and a deletion of three nucleotides (c.1390_1392del, p.Glu464del) in exon 9, and two previously reported frameshift variants; c.692_693delAG, in exon 6 and c.11dupC in exon 1.

Conclusions: Although all patients had characteristic manifestations of lipoid proteinosis, we observed intrafamilial phenotypic variability. Our data expand the pathogenic variant spectrum of *ECM1* and also supports the fact that exon 6 is one of the most common hot spots of pathological variants in *ECM1*.

KEYWORDS
ECM1, extracellular matrix protein 1, lipoid proteinosis, pathogenic variant

1 | INTRODUCTION

Lipoid proteinosis (LP) is a rare autosomal recessive genodermatosis (OMIM 247100), characterized by deposition of an amorphous hyaline-like material in the skin, mucosa, and internal organs.[1] Since its first description by Urbach and Wiethe in 1929[2] about 500 cases have been reported worldwide.[3]

Clinically, LP is characterized by a wide range of manifestations with variable severity and a slowly progressive course.[1] In most cases, the first clinical sign is a hoarse cry or voice, which develops soon after birth or during infancy, and is caused by laryngeal infiltration.[4] Subsequently, skin and mucous membrane changes develop during the first few years of life, or even later. During childhood, the skin may be easily damaged by minor trauma or friction, resulting in

blisters and scar formation. Other cutaneous features may include waxy, yellow papules and nodules with generalized skin thickening. Hyperkeratosis may appear in regions exposed to mechanical friction, such as the hands, elbows, knees, buttocks, and axillae. Scalp involvement may lead to loss of hair, although alopecia is not a significant finding in most cases of LP. The oral mucosa is often involved with cobblestone lips, tongue or gingiva, impaired tongue mobility causing speech problems, and transient swelling and ulceration of the lips and tongue.[5] However, the classic and most easily recognizable sign is multiple beaded papules along the eyelid margins (moniliform blepharosis). Although, eyelid beading is a hallmark feature of LP, it occurs later in childhood. Extracutaneous features, including short stature and neuropsychiatric abnormalities, such as dystonia, seizures, behavioral changes, and learning difficulties, have been reported in children.[6,7]

Loss-of-function pathogenic variants in the extracellular matrix protein-1 gene (*ECM1*), mapped to chromosome 1q21.2, have been identified in LP. The gene, which comprises 10 exons, encodes a secretory glycoprotein, expressed in various tissues.[8,9] It is essential for the maintenance of the skin integrity and homeostasis. In the skin, ECM1 acts as a "biological glue" that binds to perlecan, the major heparan sulfate proteoglycan of the basement membrane, as well as to growth factors and fibrillar proteins. It also contributes to the interstitial collagen fibril macro-assembly and has a substantial role in wound healing. Therefore, loss of ECM1 function within the dermis may have profound effects on dermal homeostasis, leading to the clinical features of skin infiltration, poor wound healing, scarring, and aging. On the other hand, hyaline-like accumulation within different tissues explains the other LP classic clinical findings, like hoarseness, moniliform blepharosis, and seizures.[10] To date, more than 70 pathogenic variants have been reported, including missense (12/72, 16.7%), nonsense (20/72, 27.8%), splice site (9/72, 12.5%), frameshift (31/72, 43.0%) (HGMD [2022.07.07]), and more than half of them were reported in exons 6 and 7.

Here, we report on the intrafamilial clinical variability in eight LP patients from four unrelated Arab families and add two novel variants in *ECM1* to the pathogenic variant database.

2 | MATERIALS AND METHODS

Following written informed consent (in concordance with the Declaration of Helsinki), peripheral blood samples were collected from each patient, as well as their family members. The genomic DNA was extracted from the peripheral blood samples of these cases and controls by using QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA). Polymerase chain reaction (PCR) amplification was performed with all 10 coding exons of *ECM1* (NM_004425.4, corresponding to isoform 1a, Q16610-1 comprising 540 amino acids). Sanger sequencing of all exons and adjacent intronic sections of *ECM1* were subsequently performed.

3 | RESULTS

We studied seven children and one adult from four unrelated families with clinical features of LP but intrafamilial variability (Table 1).

3.1 | Family 1

This consanguineous Libyan family included several affected members, including the proband and her younger sister (Figure 1A). The proband, an 8-year-old girl, developed hoarseness at the age of 3 months. The onset of skin lesions was at age 1 year. Multiple spontaneous blisters and erosions appeared on the face, scalp, and extremities, which healed with atrophic scars (Figure 1B,C). She suffered from recurrent ulcerations of the tongue and oral mucosa. Eyelid beading (moniliform blepharosis) was also noted. Recently, she manifested dysphagia, severe anemia and behavioral changes, but no seizures. Flexible fiber optic laryngoscopy revealed bilateral very thick vocal cords with a shortened left vocal cord. Her 5-year-old sister exhibited a milder phenotype. Subtle skin lesions, in the form of a few scattered blisters and hemorrhagic crusts were noticed on the face and extremities, but she did not exhibit hoarseness (Table 1).

In family 1, genetic testing revealed a novel homozygous pathogenic variant c.579G>A in exon 6, which is predicted to generate a premature termination codon (PTC) (p.Trp193*) (Figure 1D). Accordingly, a truncated protein may be produced or no protein at all, due to mRNA decay. The affected sister had the same genotype, while her unaffected parents and sister were confirmed as heterozygous carriers.

3.2 | Family 2

The 8 and 6-year-old male probands of family 2 were the offspring of consanguineous Egyptian parents (Figure 2A). The disease showed a very similar course in the two siblings (Table 1). The older sibling, patient 3, presented with hoarseness and recurrent multiple skin lesions. A weak and hoarse cry was the first symptom during early infancy, followed by recurrent severe oral ulcers. Skin lesions appeared at the age of 2 years, beginning with papules and erosions on the face and spreading to the scalp, trunk, and extremities, healing with atrophic scars. No neurological or psychiatric deficits or symptoms were observed in this patient. The proband's parents were clinically unaffected while his younger brother, patient 4 appeared very similar, but with milder clinical manifestations. They both had average growth and normal developmental histories.

Physical examination in patient 3 was notable for multiple yellow-white beaded papules on the margins of the bilateral upper and lower eyelids (Figure 2B). Recurrent ulcerations healing with atrophic scars were dispersed all over the body, especially the trunk and extremities. The lips and tongue were enlarged with thickened mucosa and multiple ulcers (Figure 2C). The patient's voice was remarkably hoarse.

TABLE 1 Clinical and genetic features

Clinical features	Patient 1 (8y, F)	Patient 2 (5y, F)	Patient 3 (8y, M)	Patient 4 (6y, M)	Patient 5 (39y, M)	Patient 6 (11y, M)	Patient 7 (7y, F)	Patient 8 (4y, M)
Hoarseness of voice	+ Since age of 3 months	−	+ Early infancy	+ Early infancy	+ Early childhood	+	+	+ Early infancy
Blisters with crusts	+	+	−	−	−	−	+	+
Erosive papules	−	−	+	+	−	−	+	−
Atrophic scarring	+	−	+	+	−	−		+
Moniliform blepharosis	+	−	+	+	+	+	+	+
Ulcerations on the tongue and oral mucosa	+	−	+	+	−	−	−	+
Thickened tongue	+	−	+ Inability to protrude tongue	+ Inability to protrude tongue	−	−	−	+
Bilateral vocal cords with infiltration	+ Bilateral very thick vocal cords with shortened left vocal cord	NA	+ Bilateral very thick vocal cords	+	+	NA	NA	−
Edema of endolaryngeal mucosa or vocal cords	−	−	−	−	+ with deposition of yellow submucosal material.	−	−	+
Other features	Dysphagia, severe anemia, behavioral changes	−	High IgE level	−	Nearly complete aphonia	Learning difficulties	−	Lax and wrinkled skin on the neck
Genetic findings ECM1 variant (homozygous)	c.579G>A	c.579G>A	c.692_693delAG	c.692_693delAG	c.1390_1392del	c.1390_1392del	c.1390_1392del	c.11dupC

Note: F, female; M, male; y, years; +, present; −, absent.

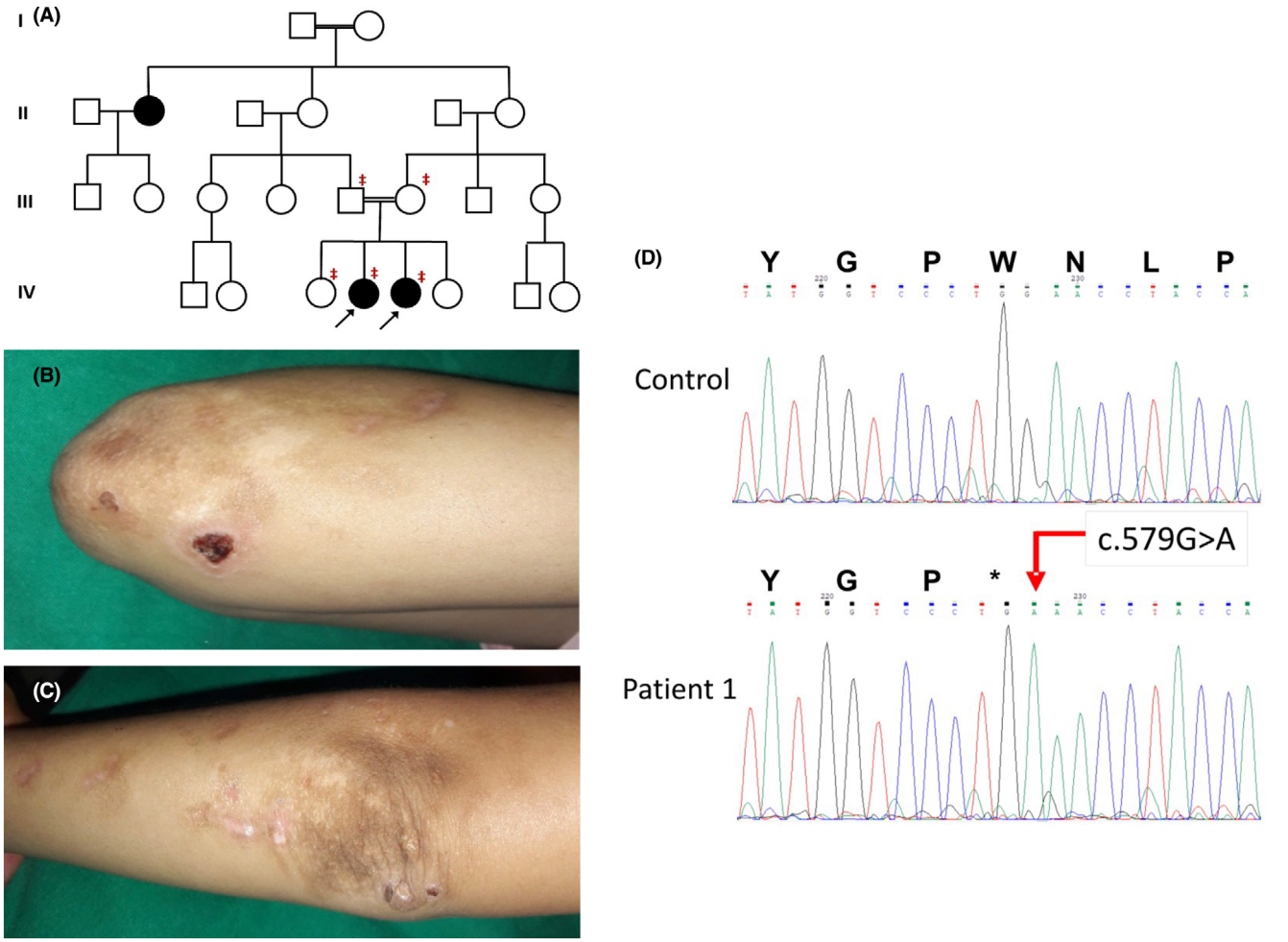

FIGURE 1 Pedigree, clinical features, and genetic finding of patient 1 in family 1. (A) Pedigree of family 1. (B) Hemorrhagic crust and atrophic scars appeared on upper extremities. (C) In patient 1, a homozygous nonsense pathogenic variant: c.579G>A, p.W193* in exon 6 was identified. ‡Means blood sample was analyzed

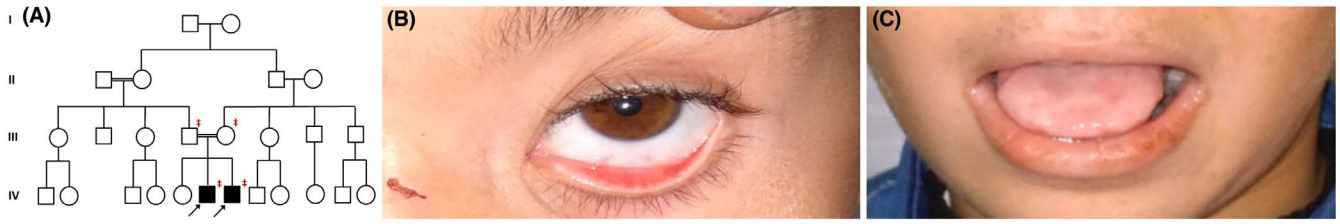

FIGURE 2 Pedigree and clinical features of family 2. (A) Pedigree of family 2. (B) The siblings presented multiple ulcerations healing with atrophic scars presented on the face. The lips were enlarged with recurrent ulcerations on their mucosal surface. The tongue was also enlarged with thickened mucosa

Direct laryngoscopy revealed bilateral very thick but mobile vocal cords with surface nodules. Brain CT detected two foci of calcification. Laboratory investigations showed elevated IgE (2840 IU/ml, normal range < 100 IU/ml), while complete blood count and liver function tests were within normal limits. Sequencing analysis identified in both siblings a homozygous 2 base pair (bp) deletion, c.692_693delAG, in exon 6 of *ECM1*. This leads to a frameshift and a PTC, p.Glu231Valfs*15, and is predicted to result either in mRNA decay, or in a truncated protein. The parents were confirmed to be heterozygous carriers of this variant.

3.3 | Family 3

This consanguineous Egyptian family, including a male adult patient (39 years old) and his two children (aged 7 and 11 years)

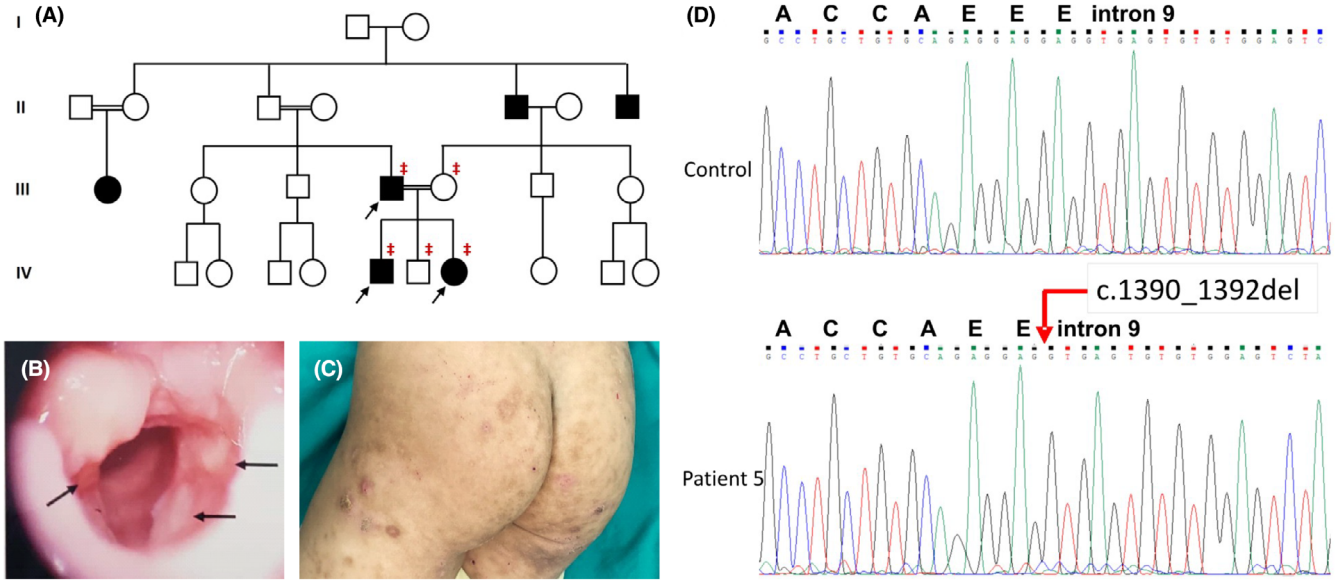

FIGURE 3 Pedigree, clinical features and genetic finding of patients in family 3. (A) Pedigree of family 3. (B) Left panel, laryngoscopy of the adult patient 5 in family 3 showed an irregular mucosal surface of both vocal cords, especially the left one; right panel, eroded papules, pustules and blisters with scars over the limbs, back, and buttocks. (C) In patient 5, variant c.1390_1392del in exon 9 was confirmed. ‡Means blood sample was analyzed

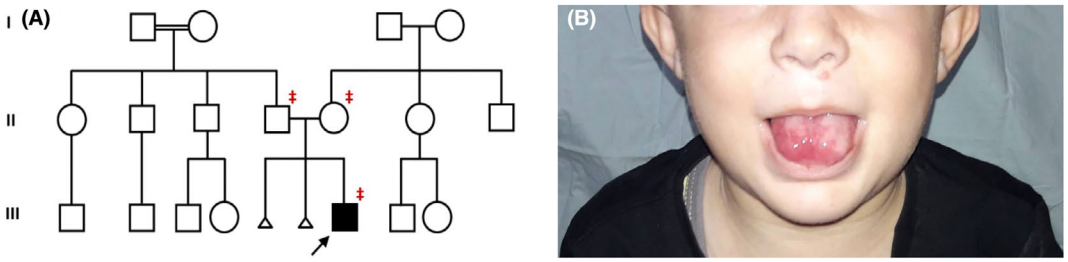

FIGURE 4 Pedigree and clinical features of patient 8 in family 4. (A) Pedigree of family 4. (B) Small ulcerations appeared on the tongue and mucosa

suffering from variable severities of LP, was referred for genetic testing (Figure 3A, Table 1). The father had a hoarse voice since early childhood, which progressed to nearly complete aphonia but without stridor or dysphagia. Laryngoscopy revealed edema of endolaryngeal mucosa, especially overlying the arytenoid, epiglottis and false vocal cords, with deposition of yellow submucosal material. Both vocal cords demonstrated an irregular mucosal surface (Figure 3B). Later, he developed relatively subtle buccal, lingual, and skin lesions pathognomonic of LP. The 11-year-old son also suffered from hoarseness, in addition to learning difficulties and very mild skin manifestations. The 7-year-old daughter presented with severe skin lesions all over the body accompanied by hoarseness of voice. Examination revealed multiple beaded papules on the eyelid margins and erosive papules, pustules and blisters with scars over the limbs, abdomen, back, and buttocks (Figure 3C).

A homozygous deletion, c.1390_1392del, in *ECM1* exon 9 was identified in the father and affected offspring. This in-frame deletion has not been reported in databases (Genome Aggregation Database, HGMD 2022.07.07). It deletes the three last nucleotides before the donor splice site of exon 9 and could generate a protein lacking glutamic acid 464, p.Glu464del or affect splicing. The proband's wife and his unaffected daughter were heterozygous carriers of this variant (Figure 3D), consistent with pseudodominant inheritance.

3.4 | Family 4

The proband was a 4-year-old boy, born to non-consanguineous Egyptian parents, who presented with persistent hoarseness and mucocutaneous lesions (Table 1, Figure 4). The 40-year-old father complained of recurrent episodes of hoarseness. A homozygous

duplication, c.11dupC, in exon 1 of *ECM1* was detected in the patient. The frameshift leads to a PTC, p.Ala5Serfs*18 in the N-terminus of ECM1. His parents were heterozygous carriers of the variant.

4 | DISCUSSION

In this study, we describe a cohort of eight cases of LP from four unrelated Arab families, one from Libya and three from Egypt, three of which were consanguineous. Seven of the affected individuals were children between 4 and 11 years of age. The only adult was the father of two affected siblings in family 3, with pseudodominant inheritance. While all patients demonstrated diagnostic features of LP, there was considerable variability in expression and severity. All the patients undergoing laryngoscopy showed either thickening or edema of both vocal cords. On the other hand, nail abnormalities were not seen in any of them. Although our clinical observations generally are in agreement with those reported from a large cohort of South African LP cases,[11] none of our patients had photosensitivity or pruritus.

The youngest in our cohort, the 4-year-old proband from family 4 was the only case that showed lax wrinkled skin. Lax, scarred and wrinkled skin, which gives rise to a prematurely aged appearance, has previously been reported in association with LP.[11,12] It has been suggested that lack of ECM1 may predispose to increased or accelerated signs of photoaging. ECM1 normally binds to matrix metalloproteinase 9 (MMP9) thereby restricting its bioactivity. If ECM1 function is reduced, then there will be increased activation of MMP9 leading to enhanced breakdown of interstitial and basement membrane collagen and hence to signs of skin aging.[13]

Among this cohort, all cases showed normal development and average cognitive function. Moreover, apart from the behavioral changes reported in the proband from family 1 and learning difficulties in the son of family 3, neither neurological deficits nor seizures were observed in any of the examined affected individuals, including the older proband from family 2 with confirmed foci of cerebral calcification. Hamie et al.[14] presented 17 cases of LP from 10 Lebanese families, and proposed a number of clinical clues to predict the clinical course of the disease. They concluded that patients with involvement of the buttocks had the most severe cutaneous clinical features and neurological involvement. However, this was not the case in our study. The 7-year-old daughter in family 3 presented with severe skin lesions and extensive lesions on her buttocks, yet she did not exhibit any neurological problems. In contrast, her brother, who suffers from some learning difficulties, showed very mild mucocutaneous lesions. However, in the current study, all except one of the patients, were in the pediatric age group. Indeed, sufficiently long follow-up will be needed before we accurately determine the clinical course in our patients.

The *ECM1* pathogenic variant database contains few recurrent pathogenic variants and most families carry unique variants except for the countries where a founder effect with one common ancestral allele has been suggested.[11] In this study, all four families had unique pathogenic variants. We identified two novel *ECM1* variants: one in exon 6 (c.579G>A, p.Trp193*) leading to a PTC, and one in exon 9 leading to an in-frame deletion of a glutamic acid within a repeat or a splicing defect (p.Glu464del, p.?). We found two known frameshift variants, c.692_693delAG, in exon 6 and c.11insC in exon 1, which were previously described in Egyptian patients.[15] In accordance with previous reports,[15–17] pathogenic variants in exon 6 were found in two out of the four studied families. To our knowledge, only a few studies described a loss-of-function variants in the first two exons,[16] or in exon 9 of *ECM1*.[18,19]

The majority of the *ECM1* pathogenic variants reported thus far are homozygous, reflecting that most cases occur in consanguineous families.[20] In this study, the identified pathogenic variants were homozygous in all the patients including the proband in family 4. In this family, although the parents denied their knowledge of any remote familial consanguinity, they were confirmed to harbor the same pathogenic variant. However, the fact that they both originate from a small town might indicate the role of a founder effect. This pathogenic variant was previously reported in other unrelated families from Egypt.

Both inter- and intra-familial clinical heterogeneity has been reported by various studies and most of them have been unable to recognize genotype–phenotype correlations.[16,17,19] Study of a large cohort, comprising 12 affected individuals from three Iranian families with an identical *ECM1* pathogenic variant, revealed extensive phenotypic variability.[20] This observation may suggest a role for genetic and epigenetic factors as well as environmental modulation of the phenotype. Furthermore, a detailed analysis of a large, inbred South African family demonstrated that individuals sharing the same genetic background can present vastly different phenotypes during disease progression.[11] In this cohort, intrafamilial variability was evident in family 3, with a mild phenotype observed in the father and son, while the daughter exhibited severe cutaneous manifestations.

Recent reports argue against an obvious genotype–phenotype correlation for *ECM1* pathogenic variants and suggest that intra- and interfamilial variability in severity and expression of LP seems more likely.[16,19,20] There do not even appear to be any subtle differences in the severity of the mucosal or skin manifestations that correlate with any particular variant. Moreover, no specific correlation between genotype and neurological manifestations has been shown. The nature of LP, as a chronic disease with a slowly progressive course, adds more complexity to the studies of genotype–phenotype correlation. As many of the clinical features of LP only manifest fully with time, it is often difficult to compare individuals at different ages. Like others, we were unable to demonstrate phenotype–genotype correlation.

Lastly, we suggest there may be minimal clinical manifestations of LP in heterozygous carriers. In this cohort, one of the molecularly-confirmed heterozygous individuals, the 40-year-old father in family 4, suffered from recurrent attacks of hoarseness of voice and direct laryngoscopy revealed a polyp (not biopsied) on the right vocal cord, but neither skin nor eye involvement could be found. In the literature, we found only a single study that reported clinical features associated with LP in apparently unaffected individuals from affected Iranian families.[21] The authors described hoarseness in cold seasons, thickening of the tongue frenulum and firm tongue as minimal manifestations of LP in genotypically heterozygous individuals.[21] Interestingly, an old

publication, decades before the discovery of the *ECM1* gene, also reported minimal manifestations of LP in two obligate heterozygote carriers from an Iranian family.[22]

The limitations of this study are the young age of the patients and the small cohort. Lack of biopsy is another constraint.

In conclusion, this study describes two previously unreported *ECM1* variants associated with LP. Furthermore, our work emphasizes the unresolved genotype–phenotype correlations in this disease. Nonetheless, obtaining long-term phenotypic data of additional patients will increase our knowledge on genotype–phenotype correlations and natural history of LP. Careful clinical evaluation of the skin, laryngoscopy, ophthalmologic and neurological examinations and follow-up should support the diagnosis that can be validated by genetic testing.

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CONFLICT OF INTEREST

The authors declare no commercial or financial conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT

Patient consent was obtained for publication of the clinical pictures.

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