ORIGINAL REPORT



# Epidermolysis Bullosa Simplex with Mottled Pigmentation and Migratory Circinate Erythema: Distinct Subtypes or a Continuum?

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**Epidermolysis bullosa simplex with mottled pigmentation (EBS-MP) or with migratory circinate erythema (EBS-MCE) are rare clinical subtypes, typically associated with *KRT5* pathogenic variants. A clinical and molecular analysis was conducted on 49 patients from 21 unrelated families in Argentina with suspected EBS-MP or EBS-MCE. Forty-eight individuals carried *KRT5* variants, with the most frequent being c.1649del, found in 44 patients from 16 families. All affected individuals inherited the variant from one parent, and shared ancestry was traced to a restricted region in northeastern Argentina. Clinical data showed early-onset blistering, followed by generalized mottled pigmentation, and progressive nail dystrophy. Migratory erythema was observed in 18 patients, resolving by age 4 in most cases. Strikingly, 3 families showed intrafamilial phenotypic variability: some individuals developed only MP, while others exhibited early MCE that later evolved into MP. This suggests a dynamic phenotypic spectrum potentially influenced by modifier factors. Additionally, a novel pathogenic variant in *KRT14* and a large *KRT5* exon 8 deletion were identified. This study represents the first report on the molecular epidemiology of EBS-MP in a South American population with an uncharacterized genetic background, contributing novel insights into genotype–phenotype correlations and natural history of EBS-MP and EBS-MCE.**

*Key words:* epidermolysis bullosa simplex; migratory circinate erythema; mottled pigmentation.

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## SIGNIFICANCE

Epidermolysis bullosa simplex is a rare genetic skin condition. Two rare forms of epidermolysis bullosa simplex – 1 with ring-shaped red patches and another with mottled pigmentation – were thought to be separate entities. In this study, we found that both patterns can appear in people from the same family, and even in the same person, all carrying the same genetic change in the *KRT5* gene. This suggests that these forms represent different stages in the progression of the disease, rather than distinct entities. Understanding this clinical presentation helps improve diagnosis and may lead to better management for people living with epidermolysis bullosa simplex.

Epidermolysis bullosa (EB) comprises a group of hereditary skin disorders, most notably characterized by blister formation following minor trauma. EB is classified into 4 types based on the level of skin cleavage, which is directly related to the mutated gene: EB simplex (intraepidermal cleavage; *KRT5, KRT14*, *PLEC*, *KLHL24*, *DST*, *EXPH5*, *CD151* genes), junctional EB (junctional cleavage; *LAMA3*, *LAMB3*, *LAMC2*, *COL17A1*, *ITGA6*, *ITGB4*, *ITGA3*), dystrophic EB (dermal cleavage; *COL7A1*) and Kindler EB (Mixed cleavage; *FERMT1*) (1).

EB simplex (EBS) is the most common type of EB, with prevalence estimates ranging from 1.54 to 28.6 cases per million people. This wide variability may be explained, at least in part, by the fact that many mild cases likely go undetected and are thus underdiagnosed (2). Most cases are caused by dominant mutations in *KRT5* and *KRT14*, presenting in localized, intermediate, or severe forms. Localized and intermediate forms are typically associated with variants located in less conserved regions of the α-helical rod domains. In contrast, severe forms are usually linked to variants in highly conserved regions at the ends of the α-helical rod. Two additional, less common clinical subtypes of EBS have also been described: EBS with mottled pigmentation (EBS-MP) and EBS with migratory circinate erythema (EBS-MCE). Both are mostly associated with pathogenic variants located in the head or tail domains of *KRT5* (3, 4).

EBS-MP is characterized by generalized blistering and a mottled or reticulate pigmentation that gradually develops across the body surface. The pigmentation does not arise at previous blister sites, and there are no signs of inflammation. Over time, patients may also develop focal keratoses and nail thickening. This subtype was first

described by Fischer and Gedde-Dahl in 1979 (5). Since then, 34 families of various ethnic backgrounds have been reported with a heterozygous pathogenic variant (c.74C>T; p.(Pro25Leu)) located in the head domain of *KRT5* (3, 6–25). Other variants in the head domain, such as c.287G>A; p.Gly96Asp and c.289T>A; p.Phe97Ile, have also been associated with mottled pigmentation (26).

However, this phenotype is not exclusively associated with variants in the head domain. Variants in the tail domain – such as c.1649del – have been identified in 4 families (16, 27–29). This single-nucleotide deletion results in a frameshift, leading to the loss of the stop codon and the production of an abnormally elongated protein. To date, a complete deletion of exon 8 in the KRT5 gene has been reported in only 1 patient, in association with mottled pigmentation (30). Even less commonly, *KRT14* variants have also been associated with EBS-MP. The c.356T>C; p.Met119Thr variant has been reported in 2 families (31, 32), and the c.1117_1158dup variant was found *de novo* in a patient from the USA (16). Additionally, a homozygous truncating variant in *EXPH5*:c.3917C>G; p.Ser1306* has been identified in a single case, further expanding the genetic spectrum of EBS-MP (33).

EBS-MCE presents with blistering from birth, with lesions following a migratory pattern on an erythematous background. Hyperpigmentation may develop at previously blistered sites. This rare EBS subtype has been associated with the *KRT5*:c.1649del variant in 7 families (4, 16, 19, 34, 35) and in 1 of them EBS initially presented as MCE during infancy and evolved to MP in adulthood (36). A similar phenotype has also been associated with the *KRT5*:1637_1640del and the *KRT5*:c.1638_1641del variants (21, 36), both deletions causing an abnormally elongated protein. Additionally, an in-frame deletion, *KRT5*:c.1321_1332del, resulting in the deletion of 4 amino acid residues p.Lys441_Gln444del from the 2B domain of *KRT5*, has been reported (37).

## MATERIALS AND METHODS

### *Editorial policies and ethical considerations*

This study was approved by the Ethics Committee of Hospital de niños Dr. R. Gutiérrez (protocol number 16.38) and by the Ethics Committee of Hospital de Clínicas José de San Martín. Informed consent was obtained from all patients (or their parents or legal guardians).

Forty-nine patients from 21 seemingly unrelated families presenting clinical signs of EBS-MP or EBS-MCE who had been referred to the Centre for Research in Genodermatoses and Epidermolysis Bullosa (CEDIGEA) between 2009 and 2024 were included in this study. Patients were anonymized and identified using a composite code in the format a.b, where "a" denotes the family number and "b" indicates the individual patient within that family. Patients were clinically assessed, and their medical records were completed jointly with the referring physicians. The clinical classification followed the last epidermolysis bullosa consensus reclassification (1). Blood or saliva samples were collected for molecular analysis of the patients and, when available, their parents, to evaluate familial segregation. DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Sanger sequencing was performed by amplification of exons using primers designed on flanking intronic sequences (38). Sequence analysis was performed using SeqScape software (Applied Biosystems, Carlsbad, CA, USA). In samples where no variants were detected by Sanger sequencing, exome NGS was performed. Variants were named following the Human Genome Variation Society (HGVS) guidelines, based on the coding DNA reference *KRT5*:NM_000424.4 and *KRT14*:NM_000526.5. All variants identified in this study were submitted to NCBI ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). Several databases and web-based tools were used for variant pathogenicity assessment. Population frequencies were obtained from gnomAD (https://gnomad.broadinstitute.org/). Mutation taster and Franklin by Genoox (https://franklin.genoox.com) were consulted for integrative variant analysis.

## RESULTS

### *Molecular epidemiology of EBS-MP and EBS-MCE in Argentina*

Molecular studies of 49 patients clinically diagnosed with EBS-MP or EBS-MCE (21 families) revealed that 48 of them had variants in the *KRT5* gene. Only 3 patients (1.1, 2.1, and 3.1) had the most commonly reported EBS-MP variant worldwide *KRT5*:c.74C>T; p.(Pro25Leu). In all 3, the variant was found *de novo*, and they were born in 3 different regions of Argentina. The vast majority of our patients – 44 individuals from 16 unrelated families (patients 5.1–9, 6.1, 7.1–2, 8.1–2, 9.1–2, 10.1–3, 11.1–2, 12.1–5, 13.1–2, 14.1–2, 15.1–3, 16.1, 17.1–4, 18.1–2, 19.1–2, 20.1–2) – presented the less commonly reported deletion variant, *KRT5*:c.1649del (Fig. S1). This variant was present in all affected individuals tested and was absent in healthy relatives. Based on familial history, the variant was inherited from 1 of the parents in all cases. Although the patients were born in various regions across Argentina, their ancestors – those from whom they inherited the pathogenic variant – were traced to a small geographic area in northeastern Argentina, within a radius of 130 km intersecting the provinces of Corrientes, Chaco, and Formosa. It is worth mentioning that we diagnosed an EBS-MP patient (4.1) with a *de novo KRT5* variant involving a complete deletion of exon 8 and flanking regions (*KRT5*:c.1440-136_1475-183del), spanning 546 nucleotides. Additionally, only 1 patient (21.1) with EBS-MP carried a variant in *KRT14*: a *de novo* in-frame

duplication of 14 amino acids (*KRT14*:c.1121_1162dup; p.(Gln374_Leu387dup)).

*Phenotypic characteristics associated with the identified variants*

The phenotypic characteristics associated with each variant are summarized in **Table I**. In cases where only 1 patient carried a specific variant (*KRT5*:c.1440-136_1475-183del and *KRT14*:c.1121_1162dup), the table indicates presence or absence (YES/NO) of the clinical features. For variants present in multiple patients, the table shows the number of patients exhibiting each characteristic over the total with available data.

*Blisters.* Except for patient 4.1, who carried the *KRT5* exon 8 deletion and developed initial blistering at 8 months of age, all other patients presented with blisters at birth or within the first 8 days of life. Although blistering onset was delayed in patient 4.1, it was more severe and predominantly affected the hands and feet. In all 3 patients carrying the *KRT5*:c.74C>T; p.(Pro25Leu) variant, a consistent blistering pattern was noted: lesions first appeared on the buttocks, followed by the hands and feet. As of the most recent follow-up, all 3 continued to develop blisters; however, it is important to note that the oldest is only 13 years old, limiting long-term assessment. In patients carrying the c.1649del variant, blistering was predominantly acral and spontaneous during early childhood, typically up to ages 5–7. After that period, lesions occurred only in response to trauma or heat. Beyond age 15, blistering was rare.

Only 2 patients with the c.1649del variant developed atrophic scarring, both in areas previously affected by aplasia cutis (patients 5.5 and 18.2). One patient (11.2) presented with erythematous and skin-coloured papules with a verrucous appearance on the dorsal hands and thigh, localized to sites of prior trauma.

*MCE.* This was observed in 18 of 36 patients carrying the c.1649del variant. For the remaining 8 patients, clinical data from the first months of life were unavailable. Most of those affected reported pruritus along the erythematous borders. Regarding the resolution of erythema, in most cases it persisted until approximately age 4 (Fig. S2). Notably, in 3 families (Families 15, 17, and 19), all studied members presented with EBS-MCE during infancy, which later resolved and evolved into EBS-MP. In Fa-

**Table I. Phenotypic characteristics of the identified variants**

| | | *KRT5* c.74C>T; p.(Pro25Leu) | *KRT5* c.1440-136_1475-183del | *KRT5* c.1649del | *KRT14* c.1121_1162dup |
|---|---|---|---|---|---|
| Number of patients | | 3 | 1 | 44 | 1 |
| Number of families | | 3 | 1 | 16 | 1 |
| Age range (years) | | 2–13 | 19 | 1–58 | 17 |
| Mean age (years) | | 9 | 19 | 20 | 17 |
| Blistering | Age at onset | 0–2 DOL | 8 months | 0–7 DOL | At birth |
| | Predominant location | Initially on the buttocks, later involving the hands and feet | Hands and feet | Hands and feet | Generalized |
| | Severity | Mild | Severe during infancy, then mild | Mild | Mild |
| | Age at resolution | Persistent | ND | 6–15 Y | ND |
| | Scarring | – | – | 2/31 | – |
| Migratory circinate erythema | Present | – | – | 18/36 | – |
| | Severity | – | – | Mild 6<br>Moderate 7 Severe 1 | – |
| | Associated pruritus | – | – | 12/16 | – |
| | Age at onset | – | – | 0–1 Y | – |
| | Age at resolution | – | – | 4 Y | – |
| | Erythema improves with sun exposure | – | – | 3/13 | – |
| Pigment anomalies | Hyperpigmentation | 3/3 | YES | 44/44 | YES |
| | Does pigmentation correspond to prior blistered areas? | 1/2 | YES | 11/31 | NO |
| | Age at onset | 8 DOL | 8 M | 0–1 Y | ND |
| | Does pigmentation become more or less apparent over time? | More (2/2) | More | More (12/28)<br>Same (2/28)<br>Less (14/28) | ND |
| | Predominant distribution pattern | Generalized, sparing the face | Extremities | Generalized, sparing the face | Generalized, sparing the face |
| | Is hypopigmentation observed? | YES | NO | 34/35 | YES |
| Additional findings | Aplasia cutis congenita | 0/3 | NO | 6/37 | NO |
| | Oral cavity/mucosal involvement | 1/3 | NO | 3/35 | NO |
| | Palmoplantar keratoderma | 1/3 | YES | 8/34 | YES |
| | Age at onset of keratoderma | Adolescence | Adolescence | Adolescence | Adolescence |
| | Dystrophic nails feet | 0/3 | NO | 19/38 | YES |
| | Dystrophic nails hands | 0/3 | NO | 2/38 | NO |
| | Photosensitivity | 1/3 | NO | 6/19 | NO |
| | Dental anomalies | 0/3 | NO | 14/33 | NO |
| | Hair anomalies | 1/3 | Diffuse alopecia | 14/37 | NO |
| | Anaemia | 0/3 | NO | 6/35 | NO |
| | Hyperhidrosis | 0/3 | YES | 7/26 | NO |

For variants present in multiple patients, the table shows the number of patients exhibiting each characteristic over the total with available data.
DOL: days of life; ND: no data; Y: years; M: months.

milies 5, 12, and 20, we identified individuals within the same family who presented with MCE during infancy, as well as individuals who only exhibited MP without a history of MCE (see **Fig. 1** and Fig. S1).

*Pigmentary anomalies*. All patients presented with mottled pigmentation. According to patient reports, hyperpigmentation was generalized in some cases, affecting both previously blistered and unaffected skin, with consistent sparing of the face; in others, it was limited mostly to areas where blisters had previously occurred (only patient 7.1 showed facial involvement). In all patients with the c.1649del variant, hyperpigmented macules typically appeared between 2 and 10 months of age, progressively increasing until adolescence, after which hypopigmentation gradually emerged (**Figs 1** and **2**).

The patient with the *KRT5* exon 8 deletion (patient 4.1) exhibited a markedly different pigmentation pattern, with hyperpigmentation appearing exclusively at sites of previous blistering, diffuse alopecia, and plantar keratoderma. In contrast, the patient with the *KRT14*:c.1121_1162dup variant (patient 21.1) exhibited very mild mottled pigmentation (**Fig. 3**).

*Other clinical features in patients with the c.1649del variant.* Aplasia cutis congenita was observed in 6 out of 37 patients with the c.1649del variant. In 2 cases, the lesions healed with atrophic scarring. Oral cavity involvement was reported in 3 patients. Fourteen out of 33 patients showed a high susceptibility to dental caries. Plantar keratoderma was noted in 8 patients, generally mild and appearing during or after adolescence. Interestingly, this feature was more frequent in EBS-MP patients with variants other than c.1649del, despite their younger age at the time of evaluation.

Hair anomalies were also a common feature; the most frequent finding was sparse and dry hair, observed in 14 of 37 patients. Additionally, 6 of 35 patients were found to have anaemia, and several (7/26) reported episodes of hyperhidrosis, particularly of the palms and soles.

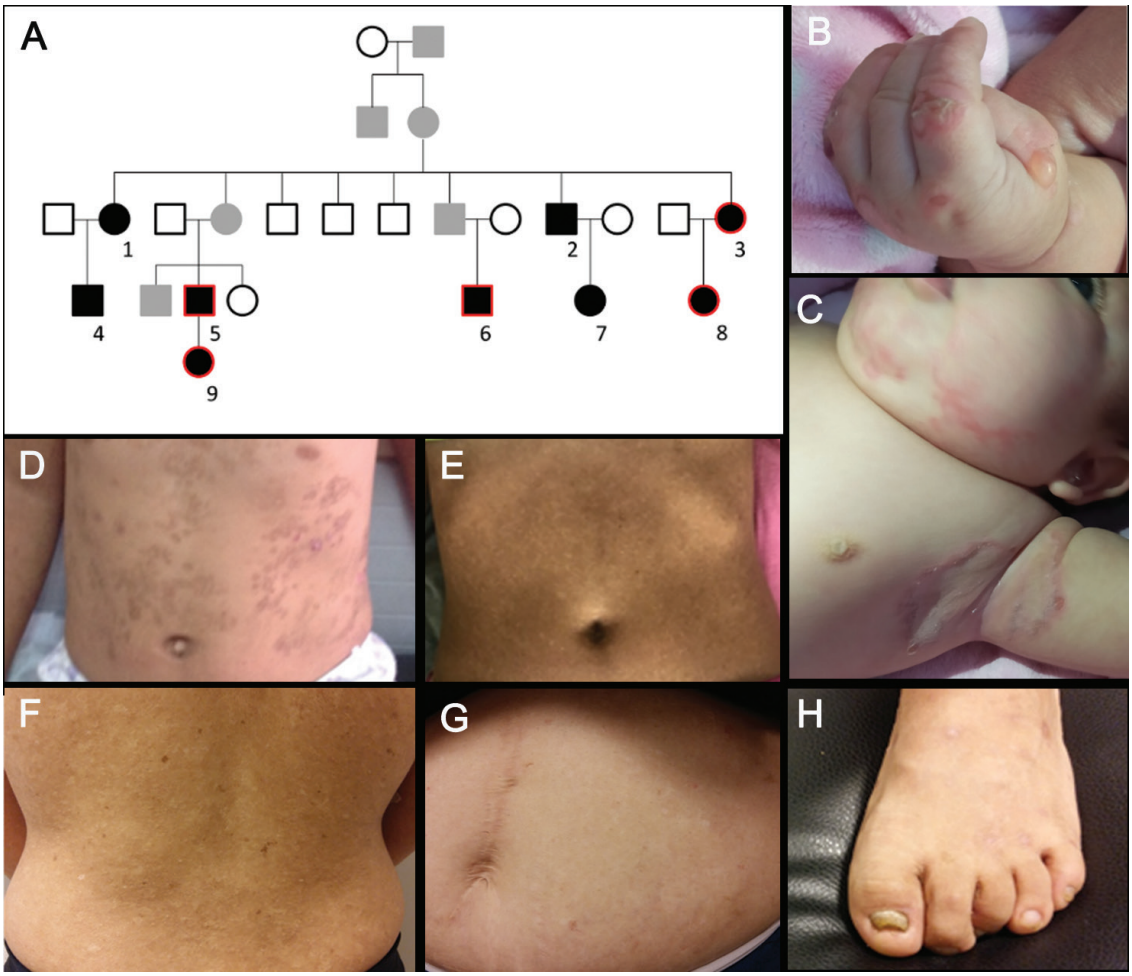


**Fig. 1. Family pedigree and age-related phenotypic features in patients with *KRT5*:c.1649del.** (A) Pedigree of Family 5. Unfilled symbols: unaffected individuals. Filled black symbols: affected individuals with only mottled pigmentation. Filled symbols with red border: affected individuals with both migratory circinate erythema and mottled pigmentation. Grey symbols: affected individuals with no data available regarding disease course. Patients with genetically confirmed *KRT5*:c.1649del variant are numbered. (B) Neonatal blisters in patient 5.9. (C) Migratory circinate erythema in patient 5.9 at 2 months of age. (D) Mottled pigmentation in patient 5.7 at age 5. (E) Mottled pigmentation in patient 5.7 at age 10. (F) Mottled pigmentation at age 20. (G) Mottled pigmentation at age 40. (H) Dystrophic nails in a patient aged 7 years.

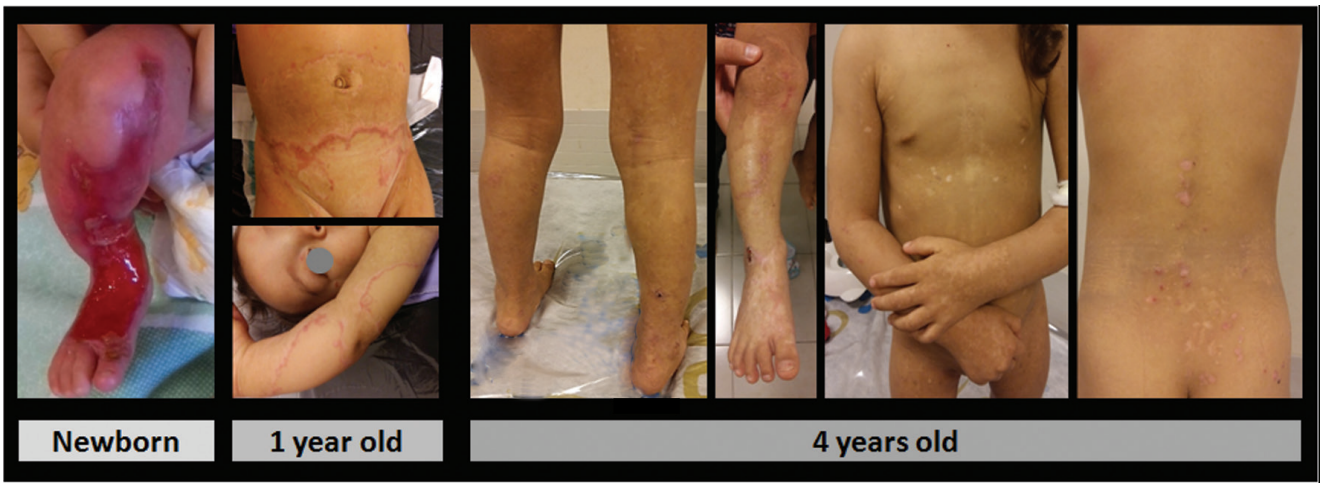


**Fig. 2. Sequential progression of migratory circinate erythema into mottled pigmentation in patient 12.4.**

We observed a distinctive progression of nail dystrophy. Dystrophy generally began at 7–10 years, first affecting the hallux toenails, then progressing to other toenails. Around age 50, fingernail involvement became apparent. In the 3 patients carrying the p.(Pro25Leu) variant, no nail dystrophy was observed; however, conclusions are premature, as none have yet reached adolescence.

## DISCUSSION

In this study, we present the molecular epidemiology, phenotypic characteristics, and disease progression of patients with EBS-MP. In our cohort, we identified only 3 patients with the most commonly reported variant in *KRT5*:c.74C>T. Due to the small number of cases – 2 entering adolescence and the third a 2-year-old – we cannot draw definitive conclusions. However, as this

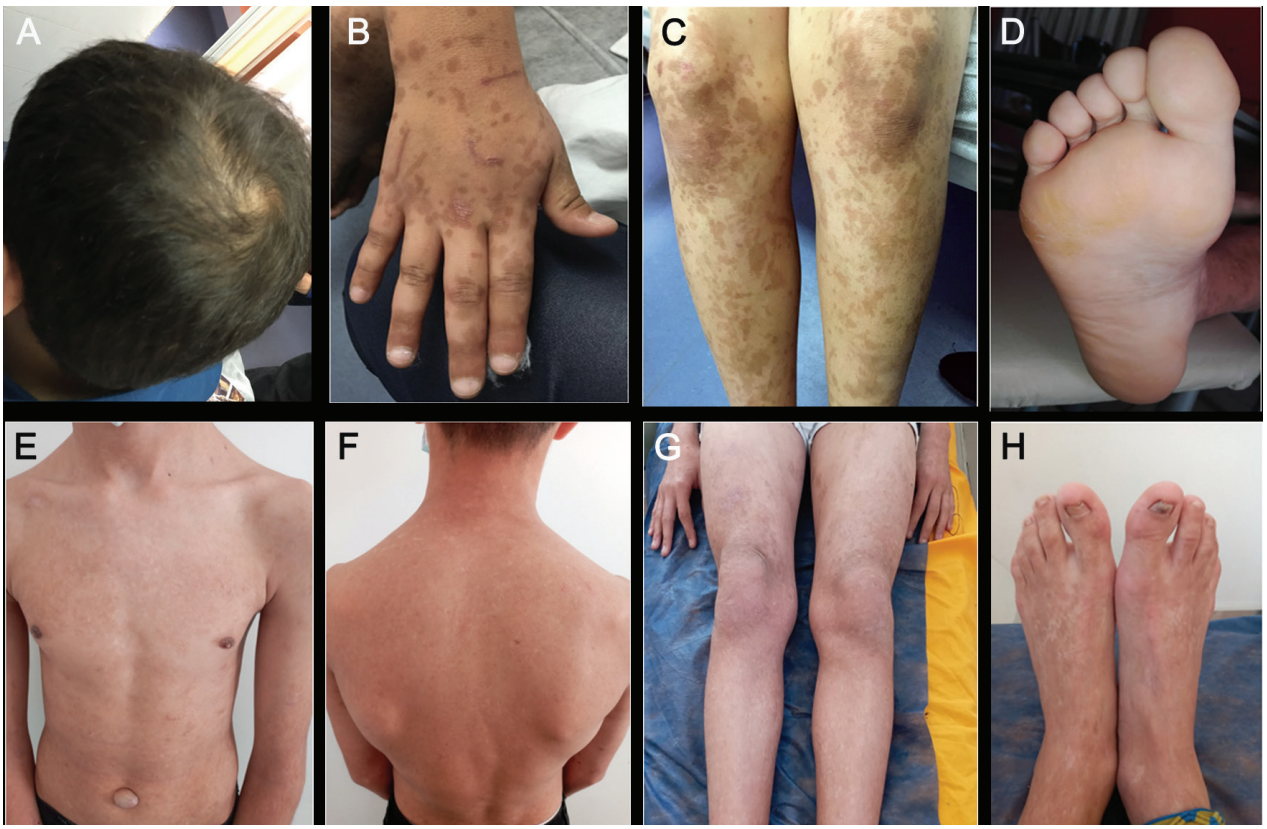


**Fig. 3. Phenotypic features.** Patient with *KRT5* exon 8 deletion (patient 4.1): (A) Diffuse alopecia. (B) Residual hyperpigmented macules on the hands. (C) Residual hyperpigmented macules on the legs. (D) Plantar keratoderma. Patient with *KRT14*:c.1121_1162dup variant (patient 21.1): (E–F) Mottled pigmentation on the trunk. (G) Mottled pigmentation on the legs. (H) Dystrophic toenail.

variant has been described multiple times previously, we can predict that these patients will follow a typical EBS-MP disease course.

We also identified a patient with a *de novo* duplication in *KRT14*:c.1121_1162dup; p.(Gln374_Leu387dup), resulting in the duplication of 14 amino acids. A similar case was reported by Arin et al. in 2010, which also presented with mottled pigmentation (16). Our finding further supports the association of duplications within the 2B domain of *KRT14* with the EBS-MP subtype.

In the patient with the 546-nucleotide deletion involving exon 8 in *KRT5*, the mottled pigmentation pattern is remarkably similar to that described by Cheng et al. (30), and notably distinct from the patterns typically observed in other variants associated with mottled pigmentation. This striking resemblance could suggest a specific genotype–phenotype correlation. However, Has et al. (39) reported a 935-nucleotide deletion also involving exon 8, but did not describe mottled pigmentation in any of the affected family members.

The majority of our patients carry the *KRT5*:c.1649del variant. This pathogenic variant was first reported by Gu et al. (34) in a Japanese girl and a Korean family with EBS-MCE, presenting with multiple vesicles on the hands, feet, and legs from birth, but without nail involvement, mucosal or ocular lesions, or palmoplantar keratoderma. Interestingly, Horiguchi et al. (27) later described a Japanese family with the same variant but a different clinical phenotype consistent with EBS-MP. In that report, pigmented spots were not considered residual post-blistering hyperpigmentation, and no circinate erythema was observed. This was interpreted by the authors as a distinct phenotype despite the same genetic variant. Subsequently, Tang et al. (28) described another family with EBS-MP carrying the same c.1649del variant. In this case, pigmentation spots were reported to fade with age, while depigmented maculae increased. Arin et al. (16) also identified this variant in patients diagnosed with either EBS-MP or EBS-MCE. Notably, Kumagai et al. (36) described a phenotype shift: patients initially presented with EBS-MCE in infancy and later evolved into an EBS-MP-like phenotype. Consistent with Kumagai's findings, all of our patients who presented with EBS-MCE in early childhood ($n=18$) eventually developed the EBS-MP phenotype, reinforcing a genotype–phenotype correlation and suggesting a dynamic clinical progression. Even more remarkably, within the same families, we observed both phenotypes: some individuals displayed EBS-MCE during infancy, evolving into EBS-MP, while others presented solely with the EBS-MP phenotype. This intra-familial variability highlights the complexity of phenotype modulation in EBS caused by the c.1649del variant.

Gu et al. (34) noted that in EBS-MCE lesions healed without scarring but with brown pigmentation. In contrast, Horiguchi et al. (37) emphasized that pigmentation in EBS-MP occurred in areas not associated with prior blistering, suggesting a different pathophysiological process. Based on these observations, we initially hypothesized that patients with MCE would show pigmentation over healed lesions, while those with MP would show more generalized pigmentation in non-lesional areas. However, our findings revealed a more complex pattern: among the 30 patients for whom we had complete clinical data, 7 individuals with EBS-MCE exhibited pigmentation restricted to areas of healed lesions. In contrast, 10 patients with the same diagnosis showed pigmentation both in areas previously affected by blistering and in unaffected skin. Among the patients without MCE, 3 presented pigmentation limited to sites of prior lesions, while 10 showed pigmentation in both lesional and non-lesional areas.

Only 1 patient presented scarring in the form of erythematous and skin-coloured warty papules over the knuckles, hands, and thighs (post-trauma), resembling the verrucous hyperkeratotic lesions described by Okamura et al. (24) in association with the *KRT5*:p.(Pro25Leu) variant.

The strength of our study lies in the longitudinal follow-up of a large group of patients from different families, all carrying the same *KRT5*:c.1649del variant. This allowed us to better characterize the natural history of the disease, provide valuable prognostic insights, and highlight the significant phenotypic variability associated with this variant. Patients typically present with mild blistering from birth through adolescence, which gradually becomes trauma- or heat-induced rather than spontaneous. Circinate migratory erythema may appear during childhood, although we were unable to identify consistent triggers or family-specific patterns. Hyperpigmentation often appears within the first months of life, especially on the limbs and abdomen, becomes more prominent during childhood and adolescence, and begins to fade in adulthood, with increasing hypopigmented macules. The number of patients across different age groups allowed us to make a notable observation: a consistent pattern of progressive nail dystrophy. Although nail dystrophy has been previously documented in patients with the p.(Pro25Leu) variant, reports of this feature in association with the c.1649del variant are scarce, likely because the observations were made in very young patients. In our cohort, all patients who reached adolescence developed dystrophic nails, initially affecting the hallux, followed by the remaining toenails, and eventually involving the great fingernails by age 50.

Recognizing the full spectrum of clinical manifestations and their progression will enhance patient counselling, guide management, and support future research into genotype–phenotype correlations and potential therapeutic interventions. As treating physicians, we also stress the importance of generating molecular epidemiological data from underrepresented populations such as ours, to

ensure that these patients are not overlooked in future research efforts and clinical trials for novel therapies.

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*The authors have no conflicts of interest to declare.*

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