Dermatological Health, 2026, Volume 4, Issue 2
http://ojs.bbwpublisher.com/index.php/DH
Online ISSN: 2981-8206
Print ISSN: 3083-4775

The P25L Mutation in the *KRT5* Gene in a Chinese Family with Epidermolysis Bullosa Simplex with Mottled Pigmentation: A Case Report and Literature Review

Daochun Fu[1,2], Ze Guo[1,2]

[1]Department of Dermatology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, China
[2]Key Laboratory of Dermatology (Anhui Medical University), Ministry of Education, Hefei 230000, Anhui, China

Abstract: *Background:* Epidermolysis bullosa simplex (EBS) with mottled pigmentation (EBS-MP; OMIM 131960) is a rare subtype of EBS that is characterized by blistering, mottled pigmentation, punctate hyperkeratosis, and dystrophic nails. It is predominantly caused by heterozygous gain-of-function mutations in the keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes. *Objective:* The purpose of this study was to identify the *KRT5* and *KRT14* gene mutations in a Chinese family affected with EBS-MP and analyze the clinical manifestations. *Methods:* Whole-exome sequencing (WES) and Sanger sequencing were performed to explore the mutations of an EBS-MP pedigree that included a 24-year-old man and his parents. *Results:* WES revealed a heterozygous c.74C>T (p.Pro25Leu) mutation in *KRT5* in the proband and his mother, which caused the substitution of proline in codon 25 with leucine (p.P25L). The same mutation was not present in the unaffected father. *Conclusion:* We confirmed the diagnosis of EBS-MP in this family, which was caused by the p.P25L mutation in *KRT5*. The proband presents additional manifestations, clinical heterogeneity of EBS-MP about skin features is acknowledged. Further observations and studies of EBS-MP are required to confirm or exclude the possible connection.

Keywords: Epidermolysis bullosa simplex; *KRT5* gene; Gene mutation

Online publication: July 10, 2026

1. Introduction

Although the study of epidermolysis bullosa simplex (EBS) in recent years is more active, epidermolysis bullosa simplex with mottled pigmentation (EBS-MP) is very rare as a subtype of EBS. EBS-MP is a rare subtype of EBS that is characterized by blistering, mottled pigmentation of the trunk and limbs, punctate hyperkeratosis of the palms and soles, and dystrophic nails [1]. Representative histological features of EBS-MP are keratinocyte degeneration and intraepidermal cleavage, while ultrastructural analysis of pigmented

areas shows abundant mature melanosomes within basal cells. EBS-MP is predominantly caused by heterozygous gain-of-function mutations in the keratin 5 (*KRT5*) and keratin 14 (*KRT14*) genes, and is inherited in either an autosomal dominant or, more rarely, an autosomal recessive manner [1,2]. Here, we report a Chinese familial case of EBS-MP caused by the p.P25L mutation in *KRT5*. In this study, we analyzed the clinical manifestations and gene mutations of an EBS-MP family, further enriching the mutation spectrum of the EBS gene and exploring the pathogenesis of EBS-MP, which promotes clinical diagnosis, prenatal screening, and gene therapy in the future.

2. Materials and methods

2.1. Ethics approval

The study was approved by the ethical committee at the First Affiliated Hospital of Anhui Medical University and all participants provided signed written informed consent.

2.2. Patient and clinical characteristics

The proband was a 24-year-old man when he first visited our institution. He showed reticulate hyperpigmentation on the trunk and extremities (**Figure 1a**), which had been noted since he was a few months old. Keratotic warty papules on the palmoplantar area and dorsum of the hand and foot (**Figure 1b**), or slight nail dysplasia were also present (**Figure 1c**). Furthermore, he also showed non-cicatricial alopecia (**Figure 1d**). A total of nine members of the family revealed similar manifestations. The family pedigree indicated an autosomal dominant genodermatosis (**Figure 1e**).

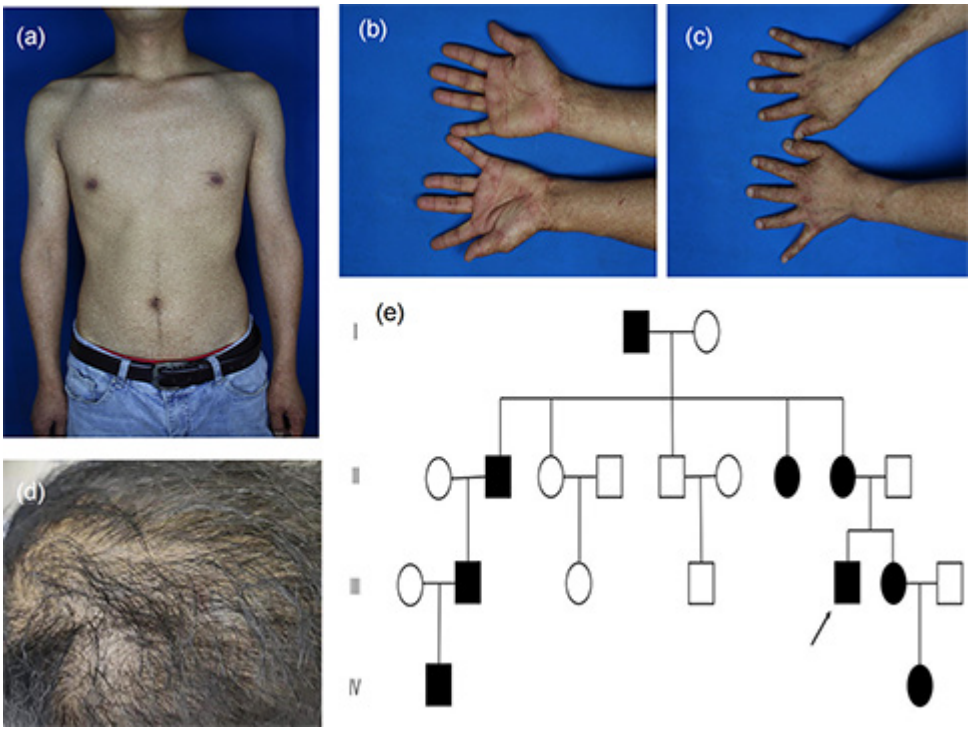

Figure 1. Patient and clinical characteristics

2.3. Gene diagnosis

Genomic DNA was extracted from peripheral blood samples obtained from the proband and his parents. DNA extraction, gene amplification, and sequence analysis were performed in Shulan Health. We performed whole-exome sequencing in the proband and his parents to comprehensively identify all genetic anomalies. Then, the mutation was confirmed by Sanger sequencing in affected members.

3. Results

3.1. Histopathological changes

Two biopsy specimens were taken from the proband, respectively from the hyperpigmented area and hypopigmented area of the left forearm. Histopathology of skin from the hyperpigmented area of the left forearm showed abundant melanocytes within the basal layer and thickened stratum corneum (**Figure 2a**). Hypopigmented area of the left forearm demonstrates reduction of melanocytes in the basal layer, increased collagen fiber, and no inflammatory cells infiltrated in the dermis (**Figure 2b–2c**).

3.2. Gene detection results

Whole-exome sequencing (WES) revealed a heterozygous C-T transition at nucleotide position 74 in the affected members, resulting in the substitution of leucine for proline residue at position 25 (P25L) in *KRT5*. The mutation was confirmed by Sanger sequencing in two affected members (**Figure 2d**).

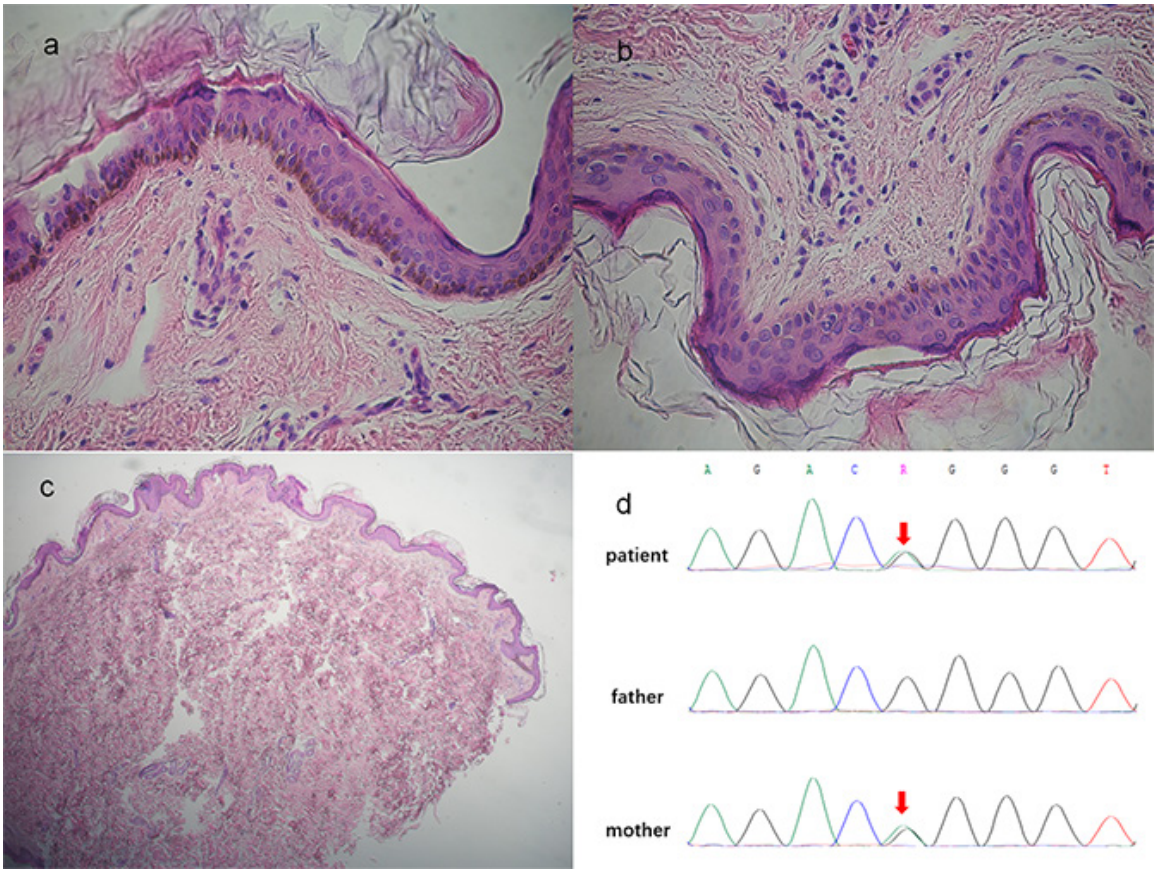

Figure 2. Histopathological changes and gene detection results

4. Discussion

EBS-MP is a rare genodermatosis with a limited number of affected members published from all over the world, first reported by Fischer and Gedd-Dahl in 1979 [3]. This study described a heterozygous mutation of the *KRT5* gene (c.74C>T) in a pedigree and analyzed the clinical characteristics and pathogenesis. In this case, the p.P25L mutation of the *KRT5* gene was found by WES. Generally, mutations in *KRT5* or *KRT14* are associated with the EBS-MP. To date, in addition to the p.P25L mutation of *KRT5*, other mutations reported to cause EBS-MP include P.G550AFSX77, and 1649delG mutations in *KRT5*, mutations of P.M119T, p.Ile373_Glu386dup, and P.I373EFSX53 of *KRT14*, with mutations of EXPH5:c.3917C>G, p.Ser1306 (**Table 1**). In all reported cases, the mutation most usually found in EBS-MP is the p.P25L mutation in *KRT5*.

Table 1. Clinical and genetic features of reported cases in the literature

Reference	*n*	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Fisher and Gedde-Dahl [3]	11(F)	at birth, upon trauma	mosaic pattern, mainly the extremities, faded with age	knees; palms	+	photosensitivity	Unknown
Verbov et al. [4]	6(F)	in infancy	predominantly extremities	palmar	+	scalp hair thinning	Unknown
Boos et al. [5]	2(F1) 7(F2)	after birth, hands and feet	particularly on the limbs	palms and soles	+	no	Unknown
Bruckner-Tuderman et al. [6]	1(S)	since birth, extremities	trunk, axillae, face and extremities.	-	+	mild photosensitivity	Unknown
Coleman et al. [7]	2(F)	since 4 months of age; in infancy	upper thighs; most of her skin	at 5 years of age, palms and soles	+	nonpruritic raised red scaly lesions， skin atrophy	Unknown
Combemale et al. [8]	1(S)	since birth, after minor trauma	over the limbs	weight-bearing areas	+	no	Unknown
Uttam et al. [9]	2(F1) 11(F2)	at birth	trunk and extremities	no	+	erosions within the oral cavity	KRT5-c.74C>T p.P25L
Irvine et al. [10]	1(S)	acral	limbs	soles	-	no	KRT5-c.74C>T p.P25L
Moog et al. [11]	3(F) 1(S)	after minor trauma; since infancy; confined to the feet	folds of the trunk, neck, arms, and legs; faded with age	-	+	photosensitivity	KRT5-c.74C>T p.P25L
Irvine et al. [12]	3(F1) 27(F2)	lifelong, exacerbation in the summer	trunk and limbs	punctate or focal palmoplantar	-	no	KRT5-c.74C>T p.P25L
Hamada et al. [13]	2(F)	after minor trauma, palms and soles	trunk and extremities	punctuate palmoplantar	-	no	KRT5-c.74C>T p.P25L
Westerhof et al. [14]	5(F)	after birth	over the body	palms and soles	+	itch	Unknown

Reference	*n*	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Yasukawa et al. [15]	2(F)	since 1 month of age, palms and soles; most of his body	axillae, the wrists, and the dorsa of the hand	axillae, the wrists, and the dorsa of the hand	-	no	KRT5-c.74C>T p.P25L
Hamada et al. [16]	1(S)	trunk, extremities, and palmoplantar skin	at the age of 9 months	-	-	no	KRT5-c.74C>T p.P25L
Horiguchi et al. [17]	6(F)	extremities and the abdomen exacerbation, in the summer season	trunk and extremities	-	+	no	KRT5-1649delG
Harel et al. [18]	1(S)	after birth	limbs and trunk, during early childhood	over the palms and soles	-	no	KRT14-c.356T>C p. M119T
Andres et al. [19]	1(F)	since infancy, after minor trauma	since birth	upper extremities and bilateral palmar	+	multiple erosions	Unknown
Tang et al. [20]	6(F)	since infancy	lower abdomen and limbs	no	+	no	KRT5-c.1649delG
Arin et al. [21]	Unknown	unknown	unknown	unknown	unknown	unknown	KRT14-c.1117_1158dup K14-p.Ile373_Glu386dup
Gray et al. [22]	1(S)	at four days of age, on the buttocks and perirectal skin, at sites of trauma, in hot and humid conditions	neck, back, and extremities, around age 2	palmoplantar	+	no	KRT14-p.I373EfsX53
Garcıá et al. [1]	6(F1) 4(F2)	plantar, in childhood	in early childhood	plantar, at a later age	+	no	KRT5-c.74C>T p.P25L
Browning et al. [23]	1(s)	since infancy	limbs and trunk	axillae, dorsal forearms	-	-	KRT5-c.74C>T p.P25L
Echeverría-García et al. [24]	3(F1) 3(F2)	f1:since birth, face and frictional areas f2:since birth	f1:axillae and groin f2: arms and legs	f1:palmoplantar f2:palms and soles	-	no	KRT5-c.74C>T p.P25L
Bchetnia et al. [25]	1(S)	since birth, extremities	limbs and trunk (2–5 mm)	soles	+	no	KRT5-c.74C>T p.P25L
Geller et al. [26]	1(S)	since birth	axilla, lower abdomen, and inguinal folds	-	-	no	KRT5-1649delG
Gerkowicz et al. [27]	1(S)	since childhood	extremities	punctate palmar	+	diffuse partial woolly hair	Unknown
Bergant et al. [28]	1(S)	since birth	whole body surface	-	-	no	KRT5-c.74C>T p.P25L

Reference	*n*	Blistering	Pigmentation	Hyperkeratosis	Nail dystrophy	Others	Mutation
Turcan et al. [2]	1(S)	since 1 year old	trunk, axillae, and proximal extremities	-	-	no	EXPH5-c.3917C>G, p.Ser1306
Nagai et al. [29]	1(F)	+	trunk and extremities	volar edgs	-	alopecia (in 4 cases)	KRT5-c.74C>T p.P25L
Okamura et al. [30]	2(F)	since birth, traumatized areas	trunk and extremities	palms and soles	+	1:alopecia 2:no	KRT5-c.74C>T p.P25L
Ferreira et al. [31]	1(S)	since birth, traumatized areas	+	-	+	photosensitivity	Unknown

F: familial cases; S: sporadic cases

Clinical manifestations of EBS-MP vary with age: the skin fragility and blisters significantly reduced with age, mottled pigmentation gradually appeared on the limbs and trunk, punctate hyperkeratosis of the palms and soles often at a later age, and nail dystrophy. Review of previous cases: blisters and bullae caused by mechanical trauma mainly occurred in the extremities, usually begin at birth or during infancy, and generally tend to disappear in adults, but can reappear in some cases. Some authors found blisters worsened in summer, but this situation is not consistently recorded (**Table 1**). Keratin 5 and 14 form the primary keratin pair of epidermal keratinocytes. Keratin molecules carrying K5-25L result in tonofilament clumping [29], this is important for K5 and K14 to form a heterodimer and assemble into intermediate filaments, suggesting that this mutation in *KRT5* results in abnormal formation of intermediate filaments, leading to abnormal perinuclear aggregation of keratin intermediate filaments. This leaves keratinocytes vulnerable and prone to rupture. Minor skin trauma, such as rubbing or scraping, can cause these cells to break down and form fluid-filled blisters and bullae.

Mottled pigmentation generally does not precede the appearance of blisters, and the area of abnormal skin pigmentation is independent of the area of blisters. In reported cases, pigmentation was described as reticulate hyperpigmentation, which in some cases may be accompanied by hypopigmented plaques (**Table 1**). The keratin head domain is known to be involved in melanosome transport [9]. This mutation in *KRT5* results in abnormality of melanosome transport, which may be responsible for the failure to transfer mature melanosomes to the neighboring keratinocytes and the large accumulation of mature melanosomes in basal cells, which accordingly explains the causes of abnormal pigmentation and hypopigmentation in patients.

Hyperkeratosis tends to occur in the palms and soles, and a small proportion of cases occur in the limbs. And it is more generalized in older patients than in youth. Abnormalities of desmosome-associated molecules such as desmoplakin and desmoglein have been proven to cause palmoplantar keratoderma (**Table 1**). The P25L mutation is located in the amino-terminal head domain of keratin 5, which contains the keratin-desmoplakin I binding sites [15]. It has been postulated that palmoplantar hyperkeratotic lesions in EBS-MP are the consequence of disruption of binding between the keratin filaments of the keratinocytes and the desmosomal proteins.

The proband presented with decreasing skin fragility with age, slowly progressive reticular hyperpigmentation over the body, focal keratinization on the palms, and marked thinning of hair. Patients of EBS-MP (included in this case) generally no longer appear tribological blisters and bullae after adulthood.

Therefore, the diagnosis of EBS-MP is difficult and needs to be differentiated from a variety of genetic diseases. The main differential diagnosis is other types of EBS, principally the herpetiformis type of Dowling-Meara (EBS-DM; OMIM 131760), Dowling-Degos disease (DDD; OMIM 179850), and Kindler syndrome (KS; OMIM 173650). Most diseases can be identified by a history of increased skin fragility in EBS-MP and genetic testing. It is noteworthy that we noticed non-cicatricial alopecia in the proband. In all reported cases, we found many cases of EBS-MP with non-cicatricial alopecia [4,27,29,30]. Therefore, we suspect that non-cicatricial alopecia is a common feature of EBS-MP that has not been noticed. Further observation is needed to confirm whether hair abnormality is a characteristic manifestation of EBS-MP.

Due to the rarity and phenotypic heterogeneity of EBS-MP, it is unknown whether the patient's other concomitant symptoms are caused by the KRT5/KRT14 mutation. Further accumulation of cases of EBS-MP can provide more accurate diagnostic criteria for genetic disorders of the KRT5/KRT14, provide valuable insights into clinical diagnosis, and assist in genetic counselling for this disease. The prognosis of EBS-MP is better with decreasing occurrence of blisters in adults, but there is no effective means of treatment for EBS-MP at present. DNA-based prenatal testing has been developed, and the disease can only be detected early by prenatal screening and prenatal diagnosis.

5. Conclusion

In this study, we identified a heterozygous c.74C>T (p.P25L) mutation in *KRT5* in a Chinese family with EBS-MP. The proband presented with reticulate hyperpigmentation, palmoplantar keratotic papules, nail dysplasia, and non-cicatricial alopecia, expanding the phenotypic spectrum of this disorder. Notably, non-cicatricial alopecia—observed in our case and multiple reported cases—may represent an underrecognized feature of EBS-MP warranting further study. Currently, no curative therapy exists for EBS-MP; management remains supportive. Genetic counseling and DNA-based prenatal diagnosis are essential for affected families. Continued accumulation of clinical and genetic data will refine diagnostic criteria and guide future targeted therapies.

Disclosure statement

The authors declare no conflict of interest.

References

[1] García M, Santiago JL, Terrón A, et al., 2011, Two Novel Recessive Mutations in *KRT14* Identified in a Cohort of 21 Spanish Families with Epidermolysis Bullosa Simplex. The British Journal of Dermatology, 165(3): 683–692.

[2] Turcan I, Pasmooij AMG, Van den Akker PC, et al., 2016, Association of Epidermolysis Bullosa Simplex with Mottled Pigmentation and *EXPH5* Mutations. JAMA Dermatology, 152(10): 1137–1141.

[3] Fischer T, Gedde-Dahl TJ, 1979, Epidermolysis Bullosa Simplex and Mottled Pigmentation: A New Dominant Syndrome. I. Clinical and Histological Features. Clinical Genetics, 15(3): 228–238.

[4] Verbov J, 1980, Hereditary Diffuse Hyperpigmentation. Clinical and Experimental Dermatology, 5(2): 227–234.

[5] Boss JM, Matthews CN, Peachey RD, et al., 1981, Speckled Hyperpigmentation, Palmo-Plantar Punctate Keratoses and Childhood Blistering: A Clinical Triad, with Variable Associations. A Report of Two Families. The

British Journal of Dermatology, 105(5): 579–585.

[6] Bruckner-Tuderman L, Vogel A, Rüegger S, et al., 1989, Epidermolysis Bullosa Simplex with Mottled Pigmentation. Journal of the American Academy of Dermatology, 21(2 Pt 2): 425–432.

[7] Coleman R, Harper JI, Lake BD, 1993, Epidermolysis Bullosa Simplex with Mottled Pigmentation. The British Journal of Dermatology, 128(6): 679–685.

[8] Combemale P, Kanitakis J, 1994, Epidermolysis Bullosa Simplex with Mottled Pigmentation. Case Report and Review of the Literature. Dermatology (Basel, Switzerland), 189(2): 173–178.

[9] Uttam J, Hutton E, Coulombe PA, et al., 1996, The Genetic Basis of Epidermolysis Bullosa Simplex with Mottled Pigmentation. Proceedings of the National Academy of Sciences of the United States of America, 93(17): 9079–9084.

[10] Irvine AD, McKenna KE, Jenkinson H, et al., 1997, A Mutation in the V1 Domain of Keratin 5 Causes Epidermolysis Bullosa Simplex with Mottled Pigmentation. The Journal of Investigative Dermatology, 108(5): 809–810.

[11] Moog U, De Die-Smulders CE, Scheffer H, et al., 1999, Epidermolysis Bullosa Simplex with Mottled Pigmentation: Clinical Aspects and Confirmation of the P24L Mutation in the *KRT5* Gene in Further Patients. American Journal of Medical Genetics, 86(4): 376–379.

[12] Irvine AD, Rugg EL, Lane EB, et al., 2001, Molecular Confirmation of the Unique Phenotype of Epidermolysis Bullosa Simplex with Mottled Pigmentation. The British Journal of Dermatology, 144(1): 40–45.

[13] Hamada T, Ishii N, Kawano Y, et al., 2004, The P25L Mutation in the *KRT5* Gene in a Japanese Family with Epidermolysis Bullosa Simplex with Mottled Pigmentation. The British Journal of Dermatology, 150(3): 609–611.

[14] Westerhof W, Dingemans KP, 2004, Generalized Mottled Pigmentation with Postnatal Skin Blistering in Three Generations. Journal of the American Academy of Dermatology, 50(5 Suppl): S65–S69.

[15] Yasukawa K, Sawamura D, Akiyama M, et al., 2005, Keratotic Lesions in Epidermolysis Bullosa Simplex with Mottled Pigmentation. Journal of the American Academy of Dermatology, 52(1): 172–173.

[16] Hamada T, Kawano Y, Szczecinska W, et al., 2005, Novel Keratin 5 and 14 Gene Mutations in Patients with Epidermolysis Bullosa Simplex from Poland. Archives of Dermatological Research, 296(12): 577–579.

[17] Horiguchi Y, Sawamura D, Mori R, et al., 2005, Clinical Heterogeneity of 1649delG Mutation in the Tail Domain of Keratin 5: A Japanese Family with Epidermolysis Bullosa Simplex with Mottled Pigmentation. The Journal of Investigative Dermatology, 125(1): 83–85.

[18] Harel A, Bergman R, Indelman M, et al., 2006, Epidermolysis Bullosa Simplex with Mottled Pigmentation Resulting from a Recurrent Mutation in *KRT14*. The Journal of Investigative Dermatology, 126(7): 1654–1657.

[19] Andres C, Chen W, Hofmann H, et al., 2009, Epidermolysis Bullosa Simplex with Mottled Pigmentation: A Case Report. International Journal of Dermatology, 48(7): 753–754.

[20] Tang HY, Du WD, Cui Y, et al., 2009, One Novel and Two Recurrent Mutations in the Keratin 5 Gene Identified in Chinese Patients with Epidermolysis Bullosa Simplex. Clinical and Experimental Dermatology, 34(8): e957–e961.

[21] Arin MJ, Grimberg G, Schumann H, et al., 2010, Identification of Novel and Known *KRT5* and *KRT14* Mutations in 53 Patients with Epidermolysis Bullosa Simplex: Correlation between Genotype and Phenotype. The British Journal of Dermatology, 162(6): 1365–1369.

[22] Gray C, Greenlaw SM, Alavian C, et al., 2011, Epidermolysis Bullosa Simplex with Mottled Pigmentation: A Novel *KRT14* Mutation. Journal of Drugs in Dermatology: JDD, 10(8): 926–927.

[23] Browning JC, Mohr B, 2012, Epidermolysis Bullosa Simplex with Mottled Pigmentation. Dermatology Online Journal, 18(1): 9.

[24] Echeverría-García BA, Vicente A, Hernández Á, et al., 2013, Epidermolysis Bullosa Simplex with Mottled Pigmentation: A Family Report and Review. Pediatric Dermatology, 30(6): e125–e131.

[25] Bchetnia M, Farez T, Lacroix J, et al., 2013, Gene Expression Analysis of Epidermolysis Bullosa Simplex with Mottled Pigmentation. Journal of Dermatological Science, 69(1): 80–82.

[26] Geller L, Kristal L, Morel KD, 2013, Epidermolysis Bullosa Simplex with Mottled Pigmentation Due to a Rare Keratin 5 Mutation: Cutaneous Findings in Infancy. Pediatric Dermatology, 30(5): 631–632.

[27] Gerkowicz A, Trüeb RM, 2014, Diffuse Partial Woolly Hair in a Patient with Epidermolysis Bullosa Simplex with Mottled Pigmentation. International Journal of Trichology, 6(2): 80–82.

[28] Bergant Suhodol An A, Drago V, 2014, Epidermolysis Bullosa Simplex with Mottled Pigmentation: The First Slovenian Case. Acta Dermatovenerologica Alpina, Pannonica, et Adriatica, 23(2): 33–34.

[29] Nagai H, Oiso N, Tomida S, et al., 2016, Epidermolysis Bullosa Simplex with Mottled Pigmentation with Noncicatricial Alopecia: Identification of a Recurrent p.P25L Mutation in *KRT5* in Four Affected Family Members. The British Journal of Dermatology, 174(3): 633–635.

[30] Okamura K, Fukushima S, Yamashita J, et al., 2019, Natural Course of Epidermolysis Bullosa Simplex with Mottled Pigmentation in a Japanese Family with the p.P25L Mutation in *KRT5*. The Journal of Dermatology, 46(7): e233–e235.

[31] Ferreira FR, Pereira CF, Moretto JC, et al., 2020, Sporadic Form of Epidermolysis Bullosa Simplex with Mottled Pigmentation. Anais Brasileiros de Dermatologia, 95(4): 536–538.