extremities. He was treated with a topical steroid and oral antihistamines; however, the number of pruritic papules and nodules gradually increased. He had no family history of skin disease and his parents were not consanguineous. Neither his parents, siblings nor two sons (42 and 49 years old) had skin complaints. He suffered from mild diabetes mellitus and benign prostate hyperplasia and had been taking anti-diabetic and herbal medicine for 1 and 2 years, respectively. Although the topical steroid and oral antihistamines provided some symptom relief, scratching and trauma induced tense bullae and pruritic prurigo-like lesions that gradually appeared mainly on the lower extremities (Fig. 1a). Multiple milia developed following blister re-epithelialization (Fig. 1b,c). He had toenail dystrophy on all toes (Fig. 1d), while his fingernails were intact. Although he had noticed toenail dystrophy in his early teens, it did not cause any inconvenience to him and he had sought no treatment for this. The mucous membranes were not affected. A skin biopsy from the leg revealed dermal–epidermal blister formation with mild lymphocyte infiltration and some eosinophil infiltration in the upper dermis, along with some milia

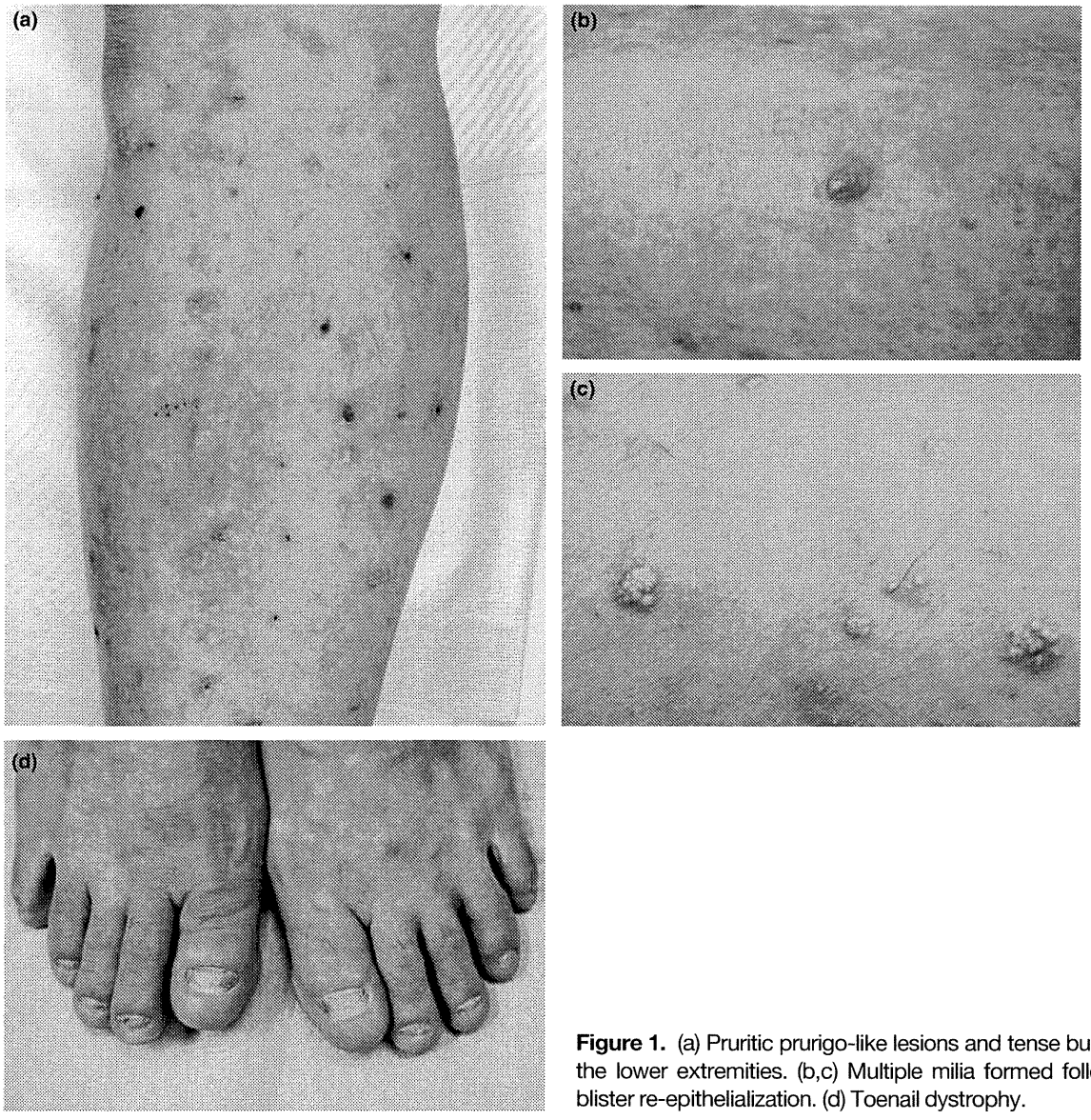

Figure 1. (a) Pruritic prurigo-like lesions and tense bullae of the lower extremities. (b,c) Multiple milia formed following blister re-epithelialization. (d) Toenail dystrophy.

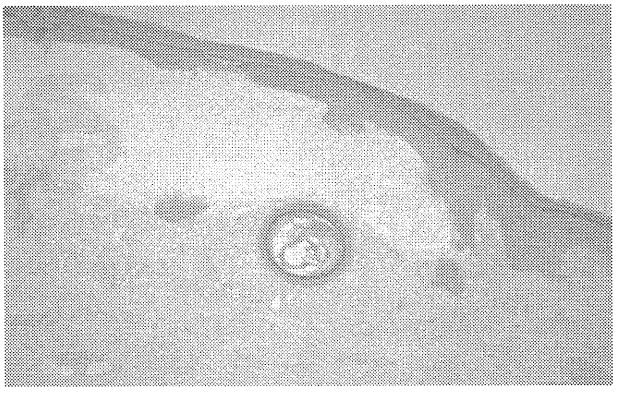

Figure 2. Histopathology of a skin biopsy from the leg. Dermal–epidermal blister formation with mild lymphocytes and partial eosinophil infiltration in the upper dermis and milia (hematoxylin–eosin, original magnification ×100).

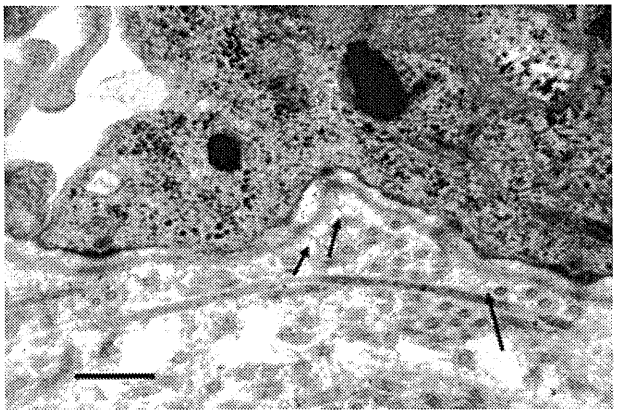

Figure 3. Electron microscopic findings from lesional and perilesional skin of the leg. Anchoring fibrils are scanty and hypoplastic (arrows) (original magnification ×40 000; scale bar, 0.5 μm).

(Fig. 2). Direct immunofluorescence (DIF) showed no immunoglobulin (Ig) or complement deposition at the basement membrane zone. Blood cell count and liver and renal function were all within normal limits. Serum IgE, ferritin and thyroid function were also within normal limits. Immunoblotting studies showed that the patient's serum did not react with any antigen. There were no abnormal findings on chest X-ray, computed tomography, electrocardiogram or upper and lower gastrointestinal endoscopy. An underlying disorder that might cause recalcitrant pruritus was not detected. To rule out drug-induced eruption, all of the drugs he was taking were discontinued and replaced with alternative drugs; however, his symptoms did not improve.

Because the results were not consistent with an autoimmune blistering disease, we examined the skin in more detail. Electron microscopy of lesional and perilesional skin of the leg revealed that anchoring fibrils were scanty and hypoplastic (Fig. 3). After informed consent, genomic DNA was extracted from his peripheral blood samples. Amplified DNA revealed a heterozygous mutation in the *COL7A1* gene, a G-to-A substitution in exon 87 (c.6859G>A; p.Gly2287Arg) (Fig. 4). This mutation has been previously reported by Shimizu *et al.*[5] Considering these findings, we diagnosed the patient with DEB-Pr. Oral prednisolone (PSL) 10 mg/day and 4,4-diamino-diphenyl-sulfone (DDS) 75 mg/day were not effective. Subsequently, PSL 30 mg/day was administrated and the pruritus became markedly

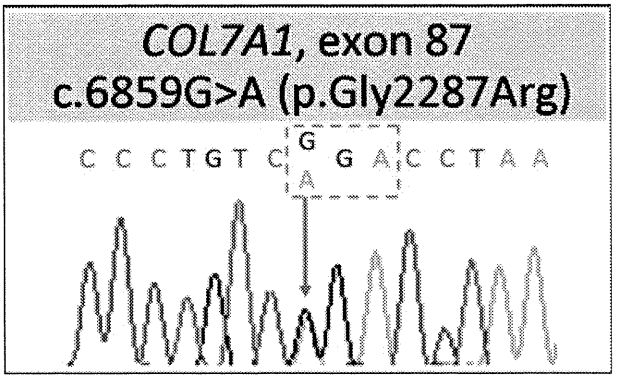

Figure 4. Amplified genomic DNA revealed a heterozygous mutation in the *COL7A1* gene, a G-to-A substitution in exon 87.

less, and no new blisters or prurigo-like lesions were seen. Nevertheless, as the blisters resolved, multiple milia ensued. The dose of PSL was tapered gradually although mild pruritus and a few blisters appeared on the shin when the PSL dose was reduced to 5 mg/day. Topical application of tacrolimus to the prurigo-like lesions also decreased his itching and was considered as effective as oral PSL for symptom control.

DISCUSSION

Dystrophic epidermolysis bullosa pruriginosa was first described by McGrath *et al.*[1] in 1994. It is a rare clinical variant of DEB, characterized by marked

Table 1. Summary of DEB-Pr patients with onset later than 20 years of age

Case No.	Age/Sex	Age at onset of DEB-Pr	Inheritance	Clinical features	Nail dystrophy	Mutation	Complications and past medical history	Treatment	Reference
1	72/M	71	Sporadic	Prurigo-like lesions and blisters with milia of bilateral legs	+	Exon 87 c.6859G>A (p.Gly2287Arg)	Diabetes and prostate hyperplasia	PSL 30 mg/day	Our case
2	34/F	29	Dominant	Pruritic, lichenoid plaques with milia	–	Exon 110 c.8137G>C (p.Gly2713Arg)	Not described	Not described	3
3	27/F	20	Dominant	Prurigo-like papules and milia of pretibial area	+	Exon73 c.6082G>A (p.Gly2028Arg)	Not described	Not described	7
4	44/F	39	Dominant	Pruritus, linear scratching lesions and hyperkeratotic, lichenoid lesions confluent into larger plaques on legs and feet	+	Exon 59 c.5264G>A (p.Gly1755Asp)	Not described	Not described	6
5	39/F	38	Dominant	Pruritus, nodular reddish prurigo-like lesions on left elbow and wrists	+	c.6900 + 4A>G	Not described	Not described	6
6	37/F	38	Dominant	Pruritus, linear scratching lesions and hyperkeratotic lichenoid lesions confluent into large gray-brown plaques on legs and feet	–	c.6900 + 2delTGAT	Not described	Not described	6
7	58/F	53	Recessive	Blistering, excoriated nodules and violaceous scars on lower legs, ankles and elbows	+	Exon 110 c.8206G>A (p.Glu2736Lys)	Diabetes and thyroid cancer	Not described	4
8	52/F	Twenties	Dominant	Intense pruritic blisters on lower legs and extensor surface of both arms	–	Exon 92 c.7097G>T (p.Gly2366Val)	Not described	Not described	8
9	52/F	25	Dominant	Pruritic blisters provoked by scratching on back, nape of the neck, elbows, and both shins	–	Exon 86 c.6752G>A (p.Gly2251Glu)	Subtotal thyroidectomy	Not described	9
10	29/F	27	Sporadic	Multiple lichenified violaceous papules, linear scarring and crusts on extensor sides of feet, lower extremities and elbows	+	Exon 110 c.8137G>C p.Gly2713Arg	Healthy	Topical corticosteroids (not effective)	10

DEB-Pr, Dystrophic epidermolysis bullosa pruriginosa; PSL, prednisolone.

pruritus, trauma-induced blistering, especially on the extensor aspect of the leg, nail dystrophy, prurigo-like lesions and multiple milia. DEB is caused by mutations in the *COL7A1* gene encoding type VII collagen, resulting in a reduced number or disorganization of anchoring fibrils. In DEB-Pr, mainly glycine substitutions have been reported.[6] The onset of clinical symptoms of DEB-Pr is typically during the first decade or even in infancy; however, in some cases clinical onset may be delayed until later in life.[3,4] From these unique clinical features, various differential diagnoses may be considered, such as prurigo nodularis, lichen planus and dermatitis artefacta.

Initially, our patient had pruritic papules and nodules mainly on the leg, which were then followed by tense bullae. Milia formation was seen after the tense bullae re-epithelialized. Our differential diagnoses included pemphigoid nodularis, prurigo nodularis, epidermolysis bullosa acquisita, DEB-Pr and a drug-induced eruption. We ruled out autoimmune blistering disease due to the results of DIF and immunoblotting analysis. Prurigo nodularis usually does not form blisters or milia. Discontinuation of the patient's medication had no clinical impact. However, the combination of the clinical features, the decreased anchoring fibrils on electron microscopy and the detection of the *COL7A1* gene led to a diagnosis of DEB-Pr. Regrettably, we could not acquire informed consent for genetic analysis from his sons; this information would be valuable for knowing whether they might also be at risk for expressing the disorder.

A summary of patients with DEB-Pr with onset later than 20 years of age is shown in Table 1.[3,4,6–10] Of note, there is a female preponderance for all late onset DEB-Pr cases, aside from our patient; the reason for this is unclear. Although the factors responsible for the variability in the time of clinical onset of DEB-Pr have not been elucidated yet, the recognition of this disease having such a late onset adds to the differential diagnosis of subepidermal blistering in elderly subjects.

Dystrophic epidermolysis bullosa pruriginosa has a wide clinical spectrum. In different pedigrees, patients with the same glycine substitution mutation may show clinical heterogeneity.[11] With regard to the pruritus, some DEB-Pr patients have elevated serum IgE and/or atopy,[3,8] but other possible associations such as functional gene promoter polymorphisms in the matrix metalloproteinase-1 (*MMP-1*), which can degrade type VII collagen,[12] and loss-of-function mutations in filaggrin (*FLG*)[4] have not improved clinicopathological understanding of disease mechanisms in DEB-Pr.

Shimizu *et al.*[5] reported a DEB pedigree with the *COL7A1* mutation p.Gly2287Arg, the same mutation as in our case. Their patients showed only nail dystrophy restricted to the great toes and did not show any signs of skin fragility. They determined that this mutation may lead to a very mild phenotype of DEB that might be overlooked. Our patient noticed toenail dystrophy in his early teens, but it was approximately 60 years more before the pruritic eruptions and cutaneous manifestations emerged. Thus, it is likely that our patient has had lifelong dominant DEB, which for most of his life only manifested as nail dystrophy, similar to the cases reported by Shimizu *et al.*[5] However, with the development of pruritus and blistering, the diagnosis evolved to DEB-Pr. Our observations therefore have important implications for the accuracy of genotype-phenotype correlation in DEB and also highlight the potential significance of pruritus in patients with DEB.

The aims of treatment for DEB-Pr are to ease the pruritus and to suppress the scratching activity that leads to the formation of blisters and/or prurigo-like lesions; however, no universally successful treatment has been established. Recent studies have described the efficacy of topical tacrolimus (as we also observed in our patient), systemic cyclosporine and thalidomide.[13–15] McGrath *et al.*[1] reported that treatment with a systemic corticosteroid 10–30 mg/day up to 2 months did not appear to be effective, whereas in our case, oral PSL 30 mg/day was effective and improved the patient's symptoms. We therefore advocate use of topical tacrolimus and a higher dose PSL as potentially useful treatment options for DEB-Pr.

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LETTER TO THE EDITOR

Dermoscopic features in a case of dyschromatosis symmetrica hereditaria

Dear Editor,

Dyschromatosis symmetrica hereditaria (DSH) is an autosomal dominant pigmentary genodermatosis caused by a mutation in *ADAR1*.[1] It is characterized by the concomitant presence of hyperpigmented and hypopigmented macules on the dorsal hands and feet.[2] The precise pathogenesis is uncertain.[2] Using dermoscopy, we found extraordinary features, which had not been described previously.

A 24-year-old Japanese man presented with a persistent pigment anomaly. Physical examination revealed a mixture of oval or round, hyperpigmented and pigmented spots 1–7 mm in diameter and irregularly shaped hypopigmented macules on the dorsal hands and feet (Fig. 1a). On the face, he had small, freckle-like hyperpigmented spots. The consanguinities had no such pigmentations. To verify the diagnosis precisely, a genetic study was performed as described previously.[3] A novel two-nucleotide deletion mutation (c.1096–1097delAA, p.K366fs) was identified and reported.[4]

We applied dermoscopy to the hyper- and hypopigmented macules on the dorsal hands. In the hyperpigmented macule, round and variously pigmented spots 0.5–1.5 mm in diameter were connected to each other, producing oval hyperpigmented macules (Fig. 1b). Interestingly, the rounded spots showed a variety of pigmented appearances, including reticulated hyperpigmented spots, diffuse pigmentation with hyperpigmented dots, reticulate pigmented spots, monotonous pigmented spots, reticulated hypopigmented spots and monotonous hypopigmented spots (Fig. 1b). The monotonous pigmented spots bore a resemblance to the dermoscopic appearance of the normal skin (Fig. 1b). In the hypopigmented lesions, round and pigmented independent spots 0.5–1.5 mm in diameter were sparsely distributed (Fig. 1c). The rounded spots showed various pigmented appearances, including reticulated pigmented spots, reticulated and monotonous pigmented spots and monotonous hypopigmented spots (Fig. 1c).

Dermoscopy revealed that the hyperpigmented macules were constructed of connected pigmented spots and that the hypopigmented lesions contained unconnected pigmented spots. The reticular pattern is commonly observed in junctional nevus or lentiginous nevus.[5] The reticulated structure in dermoscopy is known to indicate the presence of rete ridges.[5] Therefore, the monotonous pigmentation may reflect the hyperpigmentation of basal keratinocytes without the formation of rete ridges. We were unable to take a biopsy specimen from this patient and could not evaluate the correlation between the dermoscopic findings and the histopathological appearances. However, dermoscopy indicated that the melanocyte activity and the epidermal–dermal structures may vary in each spot. On the other hand, dermoscopy of ephilis shows uniform pigmentation, lentigo simplex dose a uniform pigmented reticulate network, and solar lentigo dose a faint pigmented reticulate network or uniform pigmentation.[6–8]

The dermoscopic features in DSH are different from those in Dowling–Degos disease (DDD) of the external genitalia, showing multiple hyperpigmented brownish spots with different dimensions characterized by a coarse grid of brown lines over a diffuse light-brown background.[9] In the future, it should be studied whether dermoscopy is useful for the differential diagnoses in related disorders of not only DDD but also acropigmentation reticularis Kitamura, dyschromatosis universalis hereditaria and variants.[9–12]

The *ADAR1* gene encodes adenosine deaminases acting on RNA 1 (ADAR1) which catalyze the conversion of adenosine into inosine in RNA molecules.[13] It is an important post-transcriptional mechanism for

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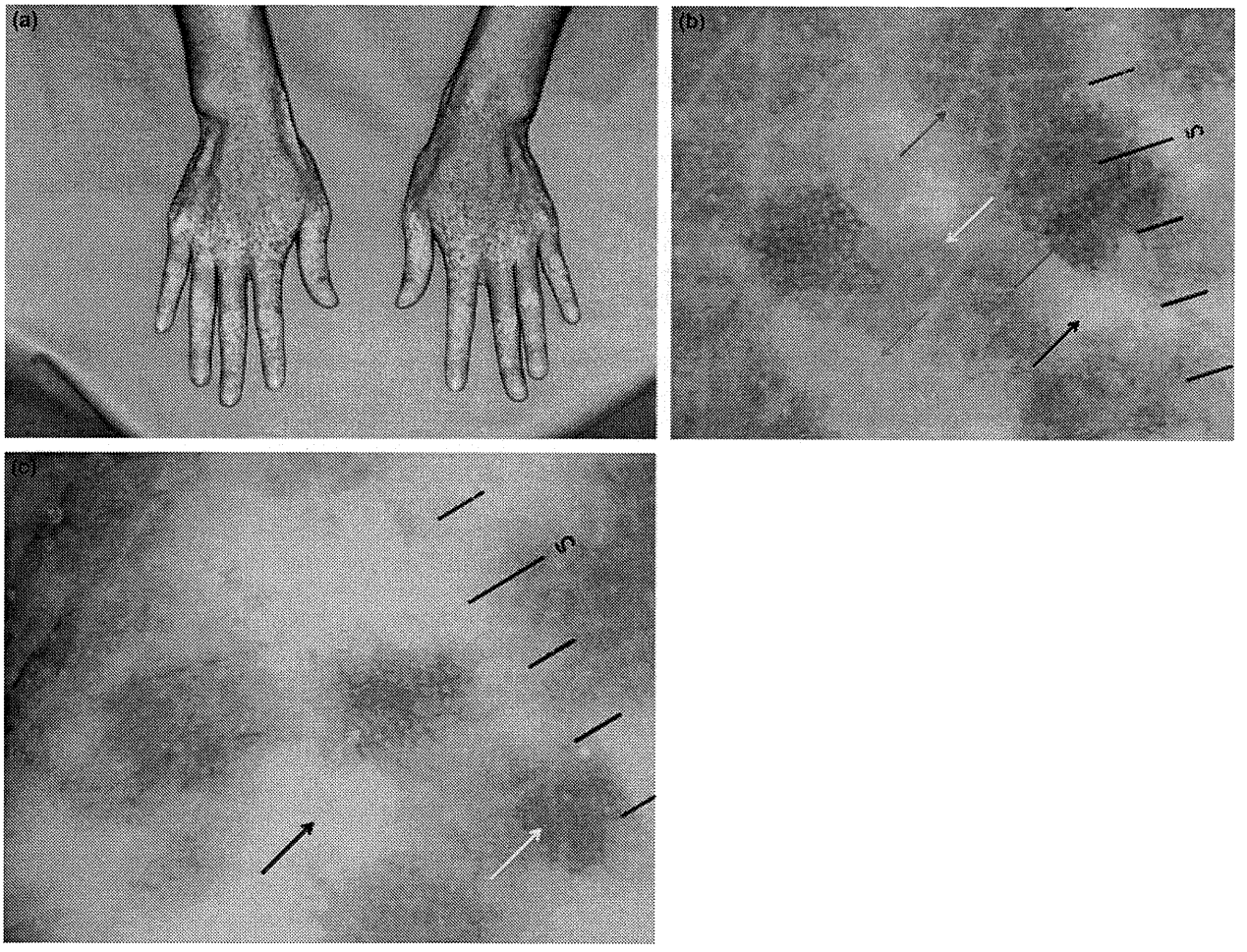

Figure 1. (a) Clinical appearance of oval or round, hyperpigmented and pigmented spots 1–7 mm in diameter and irregularly shaped hypopigmented macules on the dorsal hands. (b) On the dermoscopic examination of the hyperpigmented macule, round and variously pigmented spots 0.5–1.5 mm in diameter were connected, producing oval hyperpigmented macules. The spots were classified as follows: reticulated hyperpigmented spots (red arrow), diffuse pigmentation with hyperpigmented dots (purple arrow), reticulated pigmented spots (green arrow), monotonous pigmented spots (yellow arrow), reticulated hypopigmented spots (blue arrow) and monotonous hypopigmented spots (black arrow). (c) On the dermoscopic examination of the hypopigmented lesion, the round and pigmented independent spots 0.5–1.5 mm in diameter were sparsely distributed. The rounded spots were classified as follows: reticulated pigmented spots (green arrow), reticulated and monotonous pigmented spots (yellow arrow) and monotonous hypopigmented spots (black arrow).

generating transcript diversity.[13] We suppose that dysfunction of ADAR1 induces such various pigment appearances due to the dysregulated post-transcriptional system.

Dermoscopy in DSH showed the different characteristic of each pigmented spot, such as the degree of the pigmentation and the epidermal–dermal structure. We speculated that the pigmented spots have varied melanocyte dysfunction, aberrant melanocyte and keratinocyte interaction, and impaired construction of rete ridges.

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