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Review Article

Dyschromatosis symmetrica hereditaria and reticulate acropigmentation of Kitamura: An update

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ABSTRACT

Dyschromatosis symmetrica hereditaria (DSH) and reticulate acropigmentation of Kitamura (RAK) are rare, inherited pigmentary diseases. DSH shows a mixture of pigmented and depigmented macules on the extremities. RAK shows reticulated, slightly depressed pigmented macules on the extremities. The causative gene of DSH was clarified as *ADAR1* by positional cloning including linkage analysis and haplotype analysis in 2003. Ten years later, the causative gene of RAK was identified as *ADAM10* by whole-exome sequencing, in 2013. ADAR1 is an RNA-editing enzyme which catalyzes the deamination of adenosine to inosine (A-to-I) in double-stranded RNA substrates during post-transcription processing. Inosine acts as guanine during translation, resulting in codon alterations or alternative splice sites that lead to functional changes in proteins when they occur in coding regions. In 2012, it was clarified that *ADAR1* mutations cause Aicardi-Goutières syndrome 6, which is a severe genetic inflammatory disease that affects the brain and the skin. A zinc metalloprotease, a disintegrin and metalloprotease domain-containing protein 10 (ADAM10), is involved in the ectodomain shedding of various membrane proteins and shows various functions *in vivo*. ADAM10 is known to be involved in the ectodomain shedding of Notch proteins as substrates in the skin. We speculate that the pathogenesis of RAK and Dowling-Degos disease (DDD, a pigmentary disease similar to RAK) is associated with the Notch signaling pathway. In addition, *ADAM10* mutations proved to be associated with late-onset Alzheimer disease. This review comprehensively discusses the updated pathophysiology of those genetic pigmentary disorders.

1. Introduction

Dyschromatosis symmetrica hereditaria (DSH, MIM#127400) and reticulate acropigmentation of Kitamura (RAK, MIM#615537) are rare, inherited pigmentary disorders with characteristic distribution of the pigmentary lesions. Both disorders were first reported by Japanese dermatologists. DSH, reported by Toyama, shows a mixture of pigmented and depigmented macules on the extremities [1]. RAK, reported by Kitamura, shows reticulated, slightly depressed pigmented macules on the extremities [2]. The causative gene of DSH was clarified by positional cloning including linkage analysis and haplotype analysis in 2003 [1]. Ten years later, the causative gene of RAK was identified by whole-exome sequencing, in 2013 [2]. The former method was the conventional method before the Next-Generation Sequencing (NGS) era to find causative genes of diseases with Mendelian inheritance. The latter method has been the conventional method in the NGS era. Both methods are used when any candidate gene cannot be predicted from the pathogenetic mechanisms or malfunction of disease-associated proteins. Thus, even though the causative genes have been elucidated, the pathogeneses of those diseases have not been completely clarified. Genetics of DSH, RAK and related disorders is summarized in Table 1. This review comprehensively discusses the updated pathophysiology of those genetic pigmentary disorders.

2. Dyschromatosis symmetrica hereditaria

2.1. Clinical findings

Dyschromatosis symmetrica hereditaria (DSH, MIM#127400), also called reticulate acropigmentation of Dohi, is a pigmentation disorder that shows autosomal dominant inheritance with nearly complete penetrance. DSH was first described by Toyama in 1910, and DSH has been reported mainly in Japan and China, although

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genetically confirmed DSH cases have also been reported in Thai, Indian [3], European [4], and Hispanic [5] populations. The prevalence of DSH in Japan is estimated to be approximately 1.5 cases per 100,000 population [1].

DSH presents as a mixture of hypopigmented and hyperpigmented macules of approximately 5 mm in diameter on the dorsa of the hands and the feet (Fig. 1) and freckle-like macules on the face. 70% of patients show eruptions until the age of 7 [6]. Histopathologically, the numbers of melanocytes in hypopigmented macules are lower than in normal skin [7]. Electron microscopy has revealed the degeneration of melanocytes in the lesions [7].

As mentioned above, the causative gene of DSH—*ADAR1*, which encodes adenosine deaminase acting on RNA1 (ADAR1)—was found by using positional cloning on 111 persons, including 51 patients [1]. ADAR1 is an RNA-editing enzyme. Both familial and sporadic DSH cases with *ADAR1* mutations have been reported. More than 180 different mutations throughout *ADAR1* have been described in patients with DSH. These mutations include nonsense, missense, frameshift and splice-site mutations and are thought to lead to ADAR1 haploinsufficiency, resulting in DSH.

Genotype-phenotype correlations had not been known in DSH patients with *ADAR1* mutations, except for p.Gly1007Arg. The mutation p.Gly1007Arg was reported in DSH patients with neurological symptoms and brain calcification [8]. Recently, we evaluated the severity of skin manifestations in DSH using our severity index to find genotype-phenotype correlations [9]. For the mutations we investigated, no significant genotype-phenotype correlations were seen, although we found patients with freckle-like facial lesions to have significantly more severe symptoms on the extremities [9].

The skin manifestations on the hands of DSH patients tend to exacerbate in summer. Seasonal changes in dyschromatosis severity were analyzed quantitatively, and sun exposure was judged to be only a transiently aggravating factor [10].

2.2. ADAR1 structure and function

ADAR1 is an RNA-editing enzyme which catalyzes the deamination of adenosine to inosine (A-to-I) in double-stranded RNA substrates during post-transcription processing [11]. Inosine acts as guanine during translation, resulting in codon alterations or alternative splice sites that lead to functional changes in proteins when they occur in coding regions [11]. Recent estimates suggest that 1.6 million editing sites exist in the human genome [12]. In mammals, not only does ADAR1 edit coding RNAs, but it also edits non-coding regions, microRNAs and RNA transcripts of prolific SINE retroelements [12].

ADAR1 has two isoforms of different sizes and localizations, and their expressions are regulated by different promoters. ADAR1-p110 (110 kDa) is constitutively expressed in the nucleus, and interferon-inducible ADAR1-p150 (150 kDa) is expressed in the cytoplasm [13]. The two variants are thought to be involved in different cellular functions, including stem cell maintenance, protection against stress-induced apoptosis, and innate immune response [14–17]. Previous studies indicate that the interferon-inducible ADAR1-p150 promoter is involved in the modulation of the response to several viral infections [18].

Mutation analysis in DSH patients may give us a clue to understand the pathogenesis of DSH. Mutations in the coding region only of the p150 isoform were identified in DSH patients [19]. This finding supports the hypothesis that DSH is caused by abnormality in the p150 isoform of ADAR1 [20].

To understand the function of ADAR1, an *Adar1* knockout (KO) mouse model was established but it died at embryonic days 11.5 to 12.5 (E11.5 to E12.5) due to defects in embryonic hematopoiesis and liver disintegration [14,21]. Those results demonstrated that ADAR1 is essential to embryogenesis [14]. The $Adar^{+/-}$ mouse, which is heterozygous for Adar1 deletion, showed no skin manifestations. A selective p150-isoform-disrupted mouse, which expressed p110 normally, was generated to investigate the isoform-specific function of ADAR1 [22]. Selective disruption of p150 alone resulted in embryonic lethality from E11 to E12, similar to the time point of embryonic lethality seen previously with disruption of p110 and p150. The mouse shows no skin manifestations clinically, either [22]. An *Adar1* and *Mda5* double-KO mouse model was established, and it survived [23]. An *Adar1* and *Mavs* double-KO mouse model was established, but it died from developmental defects of the kidneys, small intestine and lymph nodes within 10 days after birth [24]. Concerning the skin, an epidermis-specific *Adar1* KO mouse model (FVB background) induced by tamoxifen was established and but it died, showing dramatically decreased aggression, thin body shape, fur loss, poor skin resiliency, skin rashes and bleeding [25]. Histopathologically, severe necrosis was seen in the epidermis of epidermis-specific *Adar1* KO mice [25]. In addition, thickening of the interfollicular epidermis and the stratum corneum were observed in epidermis-specific *Adar1* KO mice (B6 background) [25]. These results support the idea that ADAR1 plays an essential role in the epidermis.

2.3. Aicardi-Goutières syndrome: another disease caused by ADAR1 mutations

In 2012, it was clarified that *ADAR1* mutations cause Aicardi-Goutières syndrome 6 (AGS6, MIM #615010), which is a severe genetic inflammatory disease in childhood that affects the brain and the skin, and mimics viral infection [26]. In the report, 8 out of 10 AGS6 patients had bi-allelic mutations. They were the first reported patients who harbored bi-allelic *ADAR1* mutations. The relationship between A–I RNA editing efficiency and mutations in ADAR was investigated by various methods [3,26,27]. Although there are some discrepancies among the studies, we experimentally determined that the A–I RNA editing efficiency of ADAR1 remains to some degree in patients with such mutations [3]. In the

Table 1
Summary of genetics of dyschromatosis symmetrica hereditaria (DSH), reticulate acropigmentation of Kitamura (RAK) and related disorders.

Disease	Mode of inheritance	Responsible gene(s)	Mutation type	Prevalent ethnicity
DSH	autosomal dominant	*ADAR1*	truncating, missense, inframe indel	East Asian ethnicity
AGS6	autosomal recessive (autosomal dominant*)	*ADAR1*	truncating, missense	No apparent ethnic difference
RAK	autosomal dominant	*ADAM10*	truncating, missense	East Asian ethnicity
DDD	autosomal dominant	*KRT5*	truncating, missense, mutations of first codon	European ethnicity
		POFUT1	truncating, missense	
		POGLUT1	truncating, missense	
		PSENEN	truncating, missense, inframe indel	

AGS6, Aicardi-Goutières syndrome 6; DDD, Dowling-Degos disease; indel, insertion/deletion.
* Cases with ADAR1 p.Gly1007Arg mutation.

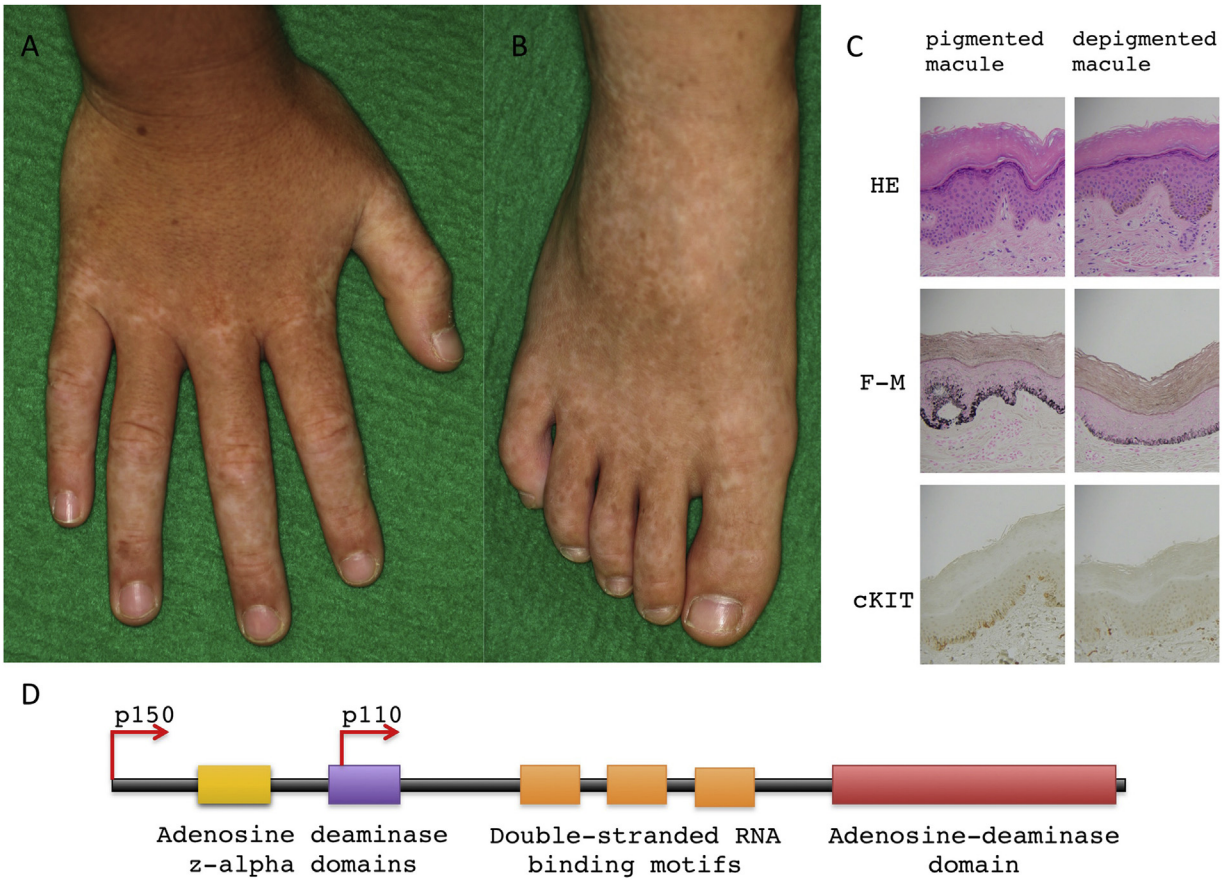

Fig. 1. Typical clinical and pathological features of dyschromatosis symmetrica hereditaria (DSH) and the domain structure of the causative gene, *ADAR1*. (A, B) A mixture of hypopigmented and hyperpigmented macules of approximately 5 mm in diameter on the dorsum of the hand (A) and the foot (A) in a representative patient with DSH. (C) Histopathologic observations of lesional skin reveals no specific morphological findings by hematoxylin-eosin staining. Fontana–Masson (F–M) staining showed little melanin in the hypopigmented macules and increased melanin pigments in the basal layer of hyperpigmented lesions along with pigmentary incontinence. Decreased numbers of melanocytes are seen in the hypomelanotic areas, compared with hypomelanotic areas, by cKIT staining. (D) A scheme of the ADAR1 protein domain structure. The two isoforms, p150 and p110, have different promoter sites and transcription initiation sites in *ADAR1*.

remaining 2 out of 10 AGS6 patients, the condition was caused by the heterozygous *ADAR1* mutation p.Gly1007Arg. As mentioned above, an identical mutation, p.Gly1007Arg, had been reported in DSH patients with neurological symptoms and brain calcification [8]. For this mutation, it was reported that the enzyme activity decrease was much greater than those for the other mutations [3,26,27]. This result suggests that the mutation p.Gly1007Arg has a dominant negative effect, and not haploinsufficiency, and that the seriously reduced A–I RNA editing efficiency is associated with the severity of the manifestations [3].

Curiously, all 10 AGS patients with *ADAR1* mutations reported in the article had no dyschromatosis on the extremities [26]. The relationship between AGS and DSH had not been elucidated completely. In 2016, the first patient with DSH associated with AGS due to a compound heterozygous *ADAR1* mutation was reported [3]. The patient was Japanese. We speculated that skin color closely relates to the phenotypic expression of DSH. Two *ADAR1* mutations previously reported as pathogenic for DSH were identified in the exome sequencing variant database of 4300 European Americans [3]. However, no Caucasian DSH patient had been confirmed by gene analysis until a report in 2018 [4], although a Hispanic case was reported in 2013 [5]. These facts suggest why DSH patients are mainly from in East Asia and support our hypothesis that the severity of DSH skin manifestations is associated with background skin color.

In addition, bi-allelic *ADAR1* mutations were revealed to cause bilateral striatal necrosis (BSN) affecting the central nervous system (CNS) in 2014, and the first DSH patient associated with BSN was reported in an Indian in 2018 [28]. The proband, with DSH and BSN, was compound heterozygous for the *ADAR1* mutation p.Pro193Ala and p.Cys1036Ser. The proband's father, with a heterozygous p.Pro193Ala mutation, showed no DSH manifestations and no DSH patients with the heterozygous p.Pro193Ala mutation had been reported previously. Furthermore, the A–I editing efficiency of ADAR1 with p.Pro193Ala was shown to be similar to that of wild-type ADAR1 [28]. These findings suggest that p.Pro193Ala is semi-pathogenic and that the heterozygous p.Pro193Ala mutation does not cause DSH manifestations [28].

The pathogenesis of DSH has not been elucidated completely. Further studies are needed to clarify the mechanisms underlying the degeneration and/or dysfunction of melanocytes in DSH and its localization to the distal extremities and the face despite the ubiquitous expression of ADAR1.

3. Reticulate acropigmentation of Kitamura (RAK)

3.1. ADAM10: the gene causative of RAK

RAK, also termed as acropigmentatio reticularis, is an infrequent hereditary pigmentation disease. In 1943, a Japanese dermatologist,

Kitamura, described a patient with RAK for the first time and, in 1953, RAK was first reported in the European literature [2]. RAK is thought to be an autosomal dominant genodermatosis with complete penetrance, though sporadic RAK patients have been described in the literature [2]. So far, more than 150 RAK patients have been described mainly in Japanese, but in every ethnicity around the world [2].

The typical clinical features are sharply demarcated, reticulate, slightly depressed brown macules without hypopigmentation, affecting the dorsa of the hands and the feet (Fig. 2) in the first or second decade of life. It was reported that RAK develops at 9.2 ± 2.2 years among genetically confirmed RAK patients, so RAK has a strong tendency to manifest before puberty [29]. The macules gradually darken and extend to the proximal regions of the extremities. The manifestations tend to progress until middle age and disappear in the patient's 70 s. The hyperpigmentation is found on the flexor aspects of the wrists, the neck, the knees and the elbows. In RAK patients, hyperpigmentation first appears on the dorsa of the hands and feet, although hyperpigmentation on the flexor aspects that is similar to that in Dowling-Degos disease also appears, as mentioned below [29]. In addition, breaks in the epidermal ridges of the palms and fingers, and palmoplantar pits are seen in RAK (Fig. 2). RAK cases associated with plantar keratoderma and partial alopecia have been reported [2].

Histopathological observations reveal thinning of the epidermis in the hyperpigmented macules of RAK. In the macules, the rete ridges are elongated and thin and, at the pointed ends of the rete ridges, pigmentation is seen. In the stratum corneum, slight hyperkeratosis without parakeratosis is observed. In the superficial dermis, only a weak inflammatory cell infiltration and no incontinentia pigmenti are seen (Fig. 2). The number of melanocytes increase in the epidermis. In keratinocytes and melanocytes in the epidermis of the macules, giant melanosomes and melanosome complexes are observed [30,31].

As RAK is rarer than DSH, it was difficult for us to recruit pedigrees large enough to provide significant linkage analysis data. The causative gene of RAK, *ADAM10*, was only found when next-generation sequencing became available. To find out mutations causative of RAK, we enlisted the cooperation of a RAK family and performed exome sequencing of 4 family members in the family using a next-generation sequencer. 53 SNV/Indels were identified as candidate mutations after several conditions were narrowed

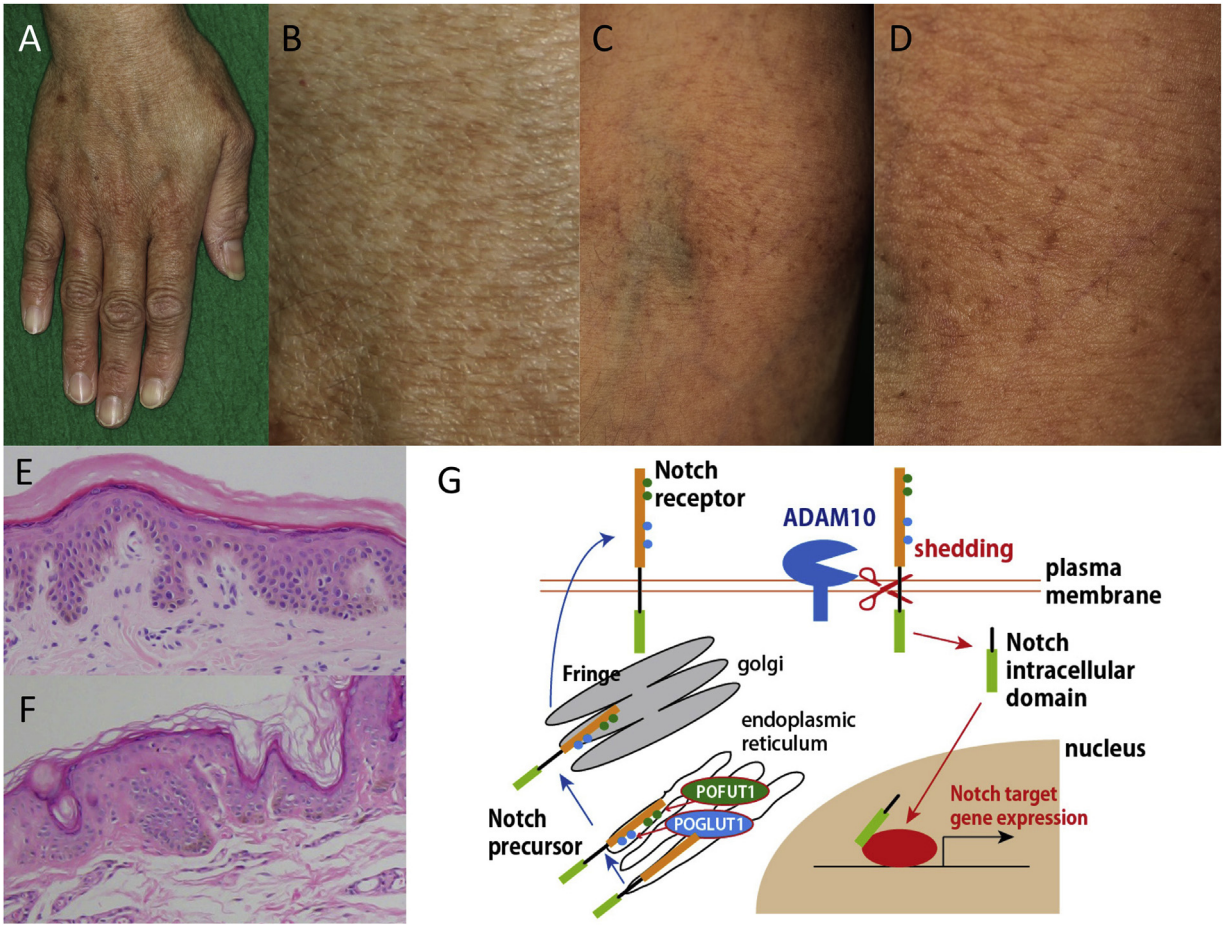

Fig. 2. Typical clinical and pathological features of reticulate acropigmentation of Kitamura (RAK) and Dowling–Degos disease (DDD), and a schematic of the roles of ADAM10, POFUT1 and POGLUT1 in the Notch pathway. (A) Sharply demarcated, reticulate, slightly depressed brown macules without hypopigmentation, affecting the dorsa of the hand. (B) High-magnification clinical photo of the RAK lesion. (C) Similar hyperpigmented macules with a reticulate pattern are seen on the cubital fossa of a DDD patient. (D) High-magnification photo of the DDD lesion. (E) Histopathologically, the brown macule of RAK shows pigmentation at the tip of the rete ridges with epidermal thinning, rete ridge elongation and thinning, and slight hyperkeratosis without parakeratosis. Only a few inflammatory cells infiltrate the dermis, and there is no pigmentary incontinence. (F) The brown macule of DDD shows acanthosis with tight digitiform rete ridges and pigmentary incontinence in the dermis. (G) ADAM10 is known to be involved in ectodomain shedding of the Notch receptor as substrates in the skin. POFUT1 (green ellipse) and POGLUT1 (blue ellipse) are both essential components of the Notch signaling pathway and are involved in the fucosylation (green dots) and glucosylation (blue dots) of the Notch precursor, respectively.

down. We confirmed the mutation status of each candidate gene of 4 other members in the family to uncover the gene that matched the phenotype of each member and the mutation status. A mutation in *ADAM10* was identified from 53 candidate mutations found in 4 initial family members. *ADAM10* encodes a zinc metalloprotease, a disintegrin and metalloprotease domain-containing protein 10 (ADAM10). The number of participating RAK family members was one-tenth that of participating DSH family members in each causative gene identification project.

So far, 6 truncating, 2 splice-site and 4 missense mutation in *ADAM10* have been detected in 23 RAK patients from 13 unrelated families. *ADAM10* loss-of-function mutations have been clearly demonstrated to be genetic defects underlying RAK. No apparent differences have been observed in RAK phenotypes depending on the nature or sites of the *ADAM10* mutations. In the patients whom we saw, no clear genotype/phenotype correlations was observed in RAK.

A disintegrin and metalloproteases (ADAMs) are a gene family of transmembrane/secreted proteins which fall into the zinc protease superfamily [32]. The ADAM family has over 40 members [32]. ADAM10 works in the ectodomain shedding of a variety of membrane proteins. Hartmann et al. created Adam10-deficient mice and found that they died at day 9.5 of embryogenesis with multiple defects in the developing central nervous system, somites and cardiovascular system [33]. ADAM10 shows various functions *in vivo*. Tissue-specific *Adam10* KO mice reveled that Adam10 is essential for the development of marginal zone B cells [34], and these mice were associated with lethal pneumonia and skin infection [35,36]. In addition, *ADAM10* mutations were proved to be associated with late-onset Alzheimer disease (LOAD) [37]. In the study, the rare, non-synonymous changes, p.Gln170His and p.Arg181Gly, were found in some families of LOAD [37] and neither p.Gln170His nor p.Arg181Gly has been identified in RAK patients.

In the skin, some molecules, including L1 cell adhesion molecule (L1-CAM), CD44, E-cadherin, N-cadherin, IL-6 receptor and CD30, are known as substrates of ADAM10 [38]. It was reported that ADAM10 haploinsufficiency lead to freckle-like macules in hairless mice [39]. Not only does the mice show freckle-like pigmentation on the dorsal aspect of the paws, but they also show diffuse pigmentation on the trunk in adults. It is noteworthy that ADAM10 haploinsufficiency alone, without the homozygous Hairless (*HR*) mutation, does not lead to the pigmentation [2]. By contrast, neither hair abnormalities nor alopecia is seen in patients with RAK. As far as we investigated, no RAK patient was found to have the *HR* mutation [2].

3.2. Reticulate acropigmentation of Kitamura and Dowling–Degos disease: Similar but distinct disorders

Dowling–Degos disease (DDD) is a very rare genodermatosis characterized by slightly depressed, sharply demarcated, dot-like or reticulate brown macules, which is very similar to RAK, mainly affecting the flexures and major skin folds. DDD shows autosomal dominant inheritance and has been described predominantly in European populations. Whether DDD and RAK are two distinct diseases or are variants of an identical clinical entity has been in controversy for a long time [2]. DDD and RAK have the similar hyperpigmented macules with a reticulate pattern. The flexures of the extremities are involved in DDD and the acral areas are affected in RAK. Overlapping patients of DDD and RAK have been reported [2]. Before identification of the causative gene of RAK, the Online Mendelian Inheritance in Man (OMIM) database had included RAK comprehensively in DDD, but now these are described as independent entities. As for Dowling–Degos disease, a linkage analysis study was done on two German families and loss-of-function mutations in *KRT5* were detected as the cause of DDD in 2006 [40]. *POFUT1* [41] and *POGLUT1* [42] were identified as additional causative genes of DDD in 2013 and 2014, respectively. Recently *PSENEN* was identified in DDD patients with acne inversa [43].

To elucidate the differences between genetically confirmed RAK patients and DDD patients, we made a comparison between the clinical and histopathological features of 11 RAK patients with *ADAM10* mutations and 6 DDD patients with *POFUT1* mutations [29]. From this study, we proposed five important clinical features for differentiating between DDD and RAK. (1) Onset age: RAK develops by the first half of the second decade of life, whereas DDD develops around or after age 20. (2) Sites of the initial skin lesions: RAK appears initially on the dorsa of the hands, whereas DDD appears on the flexure regions and the neck. (3) Comedo-like follicular papules: These suggest DDD. (4) Skin lesions on the genital region: These suggest DDD. (5) Dyschromatosis (a mixture of small hypopigmented and hyperpigmented macules in the affected skin areas): This suggests DDD. In addition, acanthosis with tight digitiform rete ridges is histopathologically seen in the skin lesions of DDD, and epidermal thinning and rete ridge narrowing characterize RAK skin lesions [29]. Furthermore, it has been noted that the RAK macules are uniformly light-brown. In contrast, the pigmentated lesions in DDD are from brown to black [44]. We speculate that this is because of pigmentary incontinence. In addition, pruritus in the skin lesions is characteristic of DDD [45].

Furthermore, in RAK, the number of melanocytes increase in the epidermis, and giant melanosomes and melanosome complexes are observed in keratinocytes and melanocytes in the epidermis of the macules [30,31]. In contrast, these features are not seen in the skin lesions of DDD [2].

ADAM10 is thought to work in the ectodomain shedding of Notch proteins as substrates in the skin. POFUT1 and POGLUT1 are both essential components of the Notch signaling pathway and are involved in the post-translational modification of Notch proteins [42]. Notch signaling plays an important role in melanocyte homeostasis [46]. Thus, we speculate that the pathogenesis of RAK and DDD is associated with the Notch signaling pathway. However, the phenotypes of RAK, DDD due to POFUT1 mutations, and DDD due to POGLUT1 mutations obviously differ from each other [47], and elucidation of the exact pathogenetic mechanisms calls for further investigation.

4. Clinical management of DSH and RAK

For DSH there are no etiologic treatments. Because suntan emphasizes the contrast between hyperpigmented and hypopigmented spots, sun-protective clothing, umbrellas and sunscreen lotions are effective to some extent [48]. There is a single case report of treatment of DSH lesions using miniature punch grafting followed by excimer light therapy [49].

For RAK there is no etiologic treatments, either. A patient was reported to have been treated with topical azelaic acid and improvement was recognized 2 months later [50]. This might be a potential treatment option, although we must take care to avoid post-inflammatory pigmentation from contact dermatitis triggered by azelaic acid.

5. Conclusion

The causative genes of DSH and RAK have been clarified as *ADAR1* and *ADAM10*, respectively. However, both ADAR1 and ADAM10 modify various substrates with various functions. In addition, the findings from patients have not always been consistent with the findings from mouse model experiments. Thus, the detailed pathogenesis of both diseases remains to be

elucidated. Indeed, we do not know why the skin manifestations are mainly seen on the extremities. Further investigations on the roles and functions of ADAR1 and ADAM10 in the skin are needed to clarify the exact pathogenetic mechanisms of DSH and RAK. We hope that information on the roles and functions of ADAR1 and ADAM10 will open doors not only to treatments for DSH and RAK, but also to those for neurological diseases such as AGS and Alzheimer disease.

Conflicts of interest

The authors have no conflict of interest to declare.

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