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Analysis of genotype/phenotype correlations in Japanese patients with dyschromatosis symmetrica hereditaria

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ABSTRACT

Dyschromatosis symmetrica hereditaria (DSH) is one of the genetic pigmentation disorders and shows characteristic mixture of hyper- and hypo-pigmented small macules on the extremities. Heterozygous mutations in the adenosine deaminase acting on RNA1 gene (*ADAR1*) cause DSH. In the present study, we report five cases of DSH and identify a distinct known mutation in each patient. Furthermore, we review previously described cases with the five *ADAR1* mutations found in the present study. We reviewed clinical and molecular findings in the present and previously reported cases and found an identical mutation can result in various phenotypic severities, even in one family. We found novel phenotype-genotype correlations between the presence/absence of facial lesions and the *ADAR1* mutation c.3286C>T. The absence of freckle-like macules in the face was found to be more commonly associated with the mutation c.3286C>T than with the other 4 *ADAR1* mutations (odds ratio = 0.056 [95% CI: 0.007–0.47, $p < 0.005$]). We objectively evaluated the severity of skin manifestations in the extremities using our definition of severity levels for such manifestations. This is the first semi-quantitative evaluation of skin manifestations in DSH. Using our definition, we found that patients with facial lesions with or without hypopigmented macules tend to show more severe symptoms on the extremities than patients without facials lesions show. Furthermore, no significant difference in the severity of the skin lesions was observed between the upper and the lower extremities, suggesting that sun exposure does not affect significantly the pathogenesis of DSH skin lesions.

Keywords: dyschromatosis symmetrica hereditaria, DSH, ADAR1, phenotype-genotype correlation, freckle-like maculey

INTRODUCTION

Dyschromatosis symmetrica hereditaria (DSH: Mendelian Inheritance in Man #127400) is one

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of the genetic pigmentation disorders. DSH is a very rare, autosomal dominantly inherited disease showing high penetrance. DSH was originally reported in Japan by a Japanese dermatologist, Ikuzo Toyama, in 1910. Later, DSH patients with other ethnicities, Koreans, Chinese, Indians, Thai and Caucasians, have been described in the literature, but most reports have been in Japanese and Chinese individuals.[1-3)]

DSH is characterized by hyperpigmented macules and hypopigmented ones on the dorsal aspects of the hands/feet, and occasionally on the arms/legs. The face is spared, apart from a few small, scattered, discrete "freckle-like" pigmented macules. It commonly develops in infancy or early childhood,[4)] then ceases spreading before adolescence and persists for the entire life.[5)]

Histopathological observations of hyperpigmented lesions have shown increased melanin pigment in the basal layer of the epidermis and pigmentary incontinence in the superficial dermis.[6)] Previous investigations of hypopigmented DSH macules have shown the degeneration of melanocytes, i.e., condensed, irregularly shaped nuclei, large vacuolization of the cytoplasm and swollen mitochondria.[6,7)]

The RNA-specific adenosine deaminase 1 gene (*ADAR1*), which encodes an RNA editing enzyme and is on chromosome 1q21.3, has been identified as responsible for DSH.[8)] Although more than 115 mutations in *ADAR1* have been reported in DSH patients,[9)] the genotype-phenotype correlation has been unclear so far.

Skin lesions of DSH are usually asymptomatic without any abnormality in the patients' general health. However, it had been reported that a few DSH cases were complicated with nervous system abnormalities.[5,10,11)] These cases had mental deterioration, brain calcification, dystonia and DSH. Two of them were revealed to carry the heterozygous p.Gly1007Arg mutation in the *ADAR1*.[5,10)]

In 2012, bi-allelic *ADAR1* mutations were shown to cause Aicardi-Goutières syndrome 6 (AGS6)[12)], a genetic inflammatory disorder of the central nervous system, which shows dystonia, mental deterioration and brain calcification. In the report, two out of the 10 reported AGS patients had the identical heterozygous mutation p.Gly1007Arg. Though DSH and AGS share the identical causative gene, all AGS patients in the report showed no dyschromatosis. Thus these two diseases were regarded as distinct disorders at that time.

In 2016, we reported the first DSH case with AGS due to bi-allelic *ADAR1* mutations.[13)] In the report, *in vitro* RNA editing activity assay was performed. p.Gly1007Arg showed severe reduction of A-I editing efficiency than the other mutations in *ADAR1*. This result seemed consistent with the phenotypic severity of DSH and AGS.

To date, the detailed pathogeneses of DSH and AGS6 remain unknown. Generally DSH occurs haploinsufficiency caused by heterozygous mutations in *ADAR1*. However, it has been thought that p.Gly1007Arg has a dominant negative effect.[12)]

We identified five *ADAR1* mutations in four Japanese multi-generation families and a sporadic patient with DSH, and by reviewing previous case reports of DSH patients with the identical ADAR1 mutations, we investigated whether any genotype-phenotype correlations exist in DSH.

MATERIALS AND METHODS

Patients

We analyzed five Japanese patients from five independent families who presented or were referred to our department in the past 8 years (Fig. 1). Table 1 summarizes the clinical and molecular findings of the DSH cases included in the present study. In some families, clinical information of all affected family members was not sufficiently available. Thus, we used only

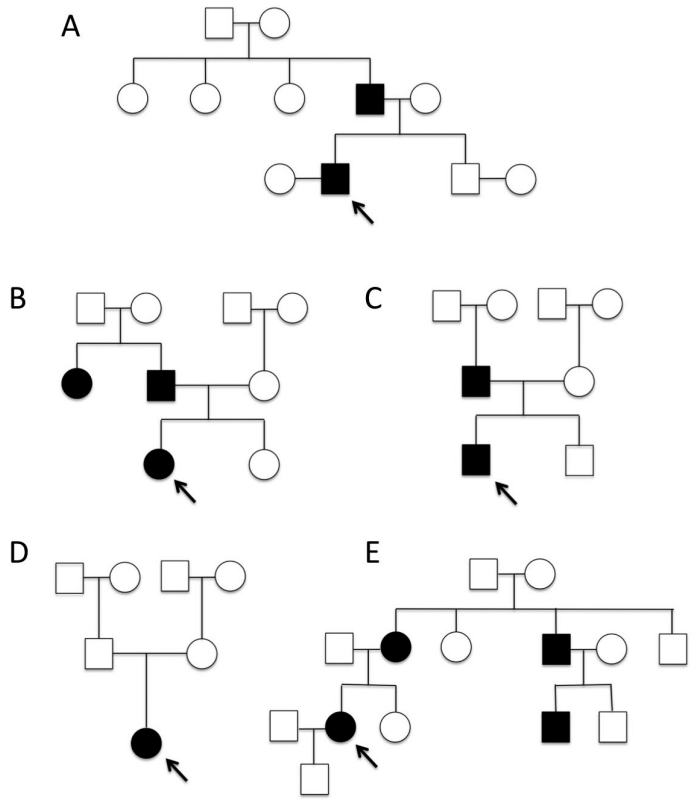

Fig. 1 Pedigrees of five families with DSH
Arrows indicate probands. The probands in Families A to E are Cases 1 to 5, respectively. Squares indicate males; circles indicate females. Closed circles and squares indicate individuals with DSH skin manifestations.

Table 1 Clinical and molecular findings in the present and previously reported DSH cases with the 5 *ADAR1* mutations

	Mutation	Family	Number of Affected Members	Ethnicity	Facial Involvement (No./Total No.)	Hypo-pigmentation on the Face (No./Total No.)
1	c.2679T>A (p.Cys893X)	1 (Family A)	1 (43 y.o. male, Case 1)	Japanese	1/1	0/1
		2	2	Japanese	1/2	1/2
2	c.3286C>T (p.Arg 1096X)	1 (Family B)	2 (5 y.o. female, Case 2) (45 y.o. male)	Japanese	2/2	0/2
		2	9	Chinese	5/9	0/9
		3	8	Chinese	3/8	0/8
		4	2	Chinese	0/2	0/2
		5	2	Chinese	2/2	0/2
		6	7	Chinese	0/7	0/7
		7	3	Japanese	3/3	0/3
		8	6	Chinese	?	?

3	c.1420C>T (p.Arg 474X)	2 (Family C)	1 (2 y.o. female, Case 3)	Japanese	1/1	1/1
		2	11	Japanese	?	Unknown
		3	1 (unknown, male)	Chinese	1/1	1/1
		4	2	Chinese	2/2	0/2
		5	1 (13 y.o. male)	Chinese	1/1	0/1
4	c.2746C>T (p.Arg 916Trp)	1	1 (34 y.o. female, Case 4)	Japanese	1/1	1/1
		2	1 (25 y.o. male)	Chinese	1/1	0/1
5	c.1601G>A (p.Gly471Aspfs X30)	1 (Family E)	1 (36 y.o. female, Case 5)	Japanese	1/1	1/1
		2	5	Chinese	5/5	0/5

Table 1 Continued

Mutation	Family	Severity of symptoms in the extremities (arms/legs)	Disease onset	Complications	Reference
1	1 (Family A)	Moderate/Severe	Before 6 y.o.	n.p.	Present study
	2	Mild/Mild	Unknown	n.p.	Kondo *et al.* 2008
2	1 (Family B)	Moderate/Severe	Before 6 y.o.	n.p.	Present study
		Severe/Severe	Before 6 y.o.	n.p.	
	2	Unknown	8 mo.–10 y.o.	n.p.	Zhang *et al.* 2004
	3	Unknown	3 y.o.–11 y.o.	n.p.	
	4	Unknown	3 mo.–8 y.o.	n.p.	Hou *et al.* 2007
	5	Mild/Mild	Unknown	n.p.	Zhang *et al.* 2008
	6	Mild/Mild	6 mo.–17 y.o.	n.p.	Li *et al.* 2010
	7	Moderate/Moderate	Unknown	n.p.	Murata *et al.* 2010
	8	Unknown	Unknown	n.p.	Wang *et al.* 2010
3	1 (Family C)	Severe/Severe	Before 6 y.o.	n.p.	Present study
	2	Unknown	Unknown	n.p.	Miyamura *et al.* 2003
	3	Unknown	6–9 y.o.	n.p.	Sun *et al.* 2005
	4	Mild/Mild	6 mo.–17 y.o.	n.p.	Li *et al.* 2010
	5	Mild/Mild	6 y.o.	n.p.	Zhang *et al.* 2013
4	1 (Family D)	Moderate/Moderate	At birth	Autoimmune hemolytic anemia	Present study
	2	Moderate/Moderate	3 y.o.	n.p.	Liu *et al.* 2004
5	1 (Family E)	Severe/Severe	4 y.o.	n.p.	Present study
	2	Mild/Mild	3–10 y.o.	n.p.	Liu *et al.* 2014

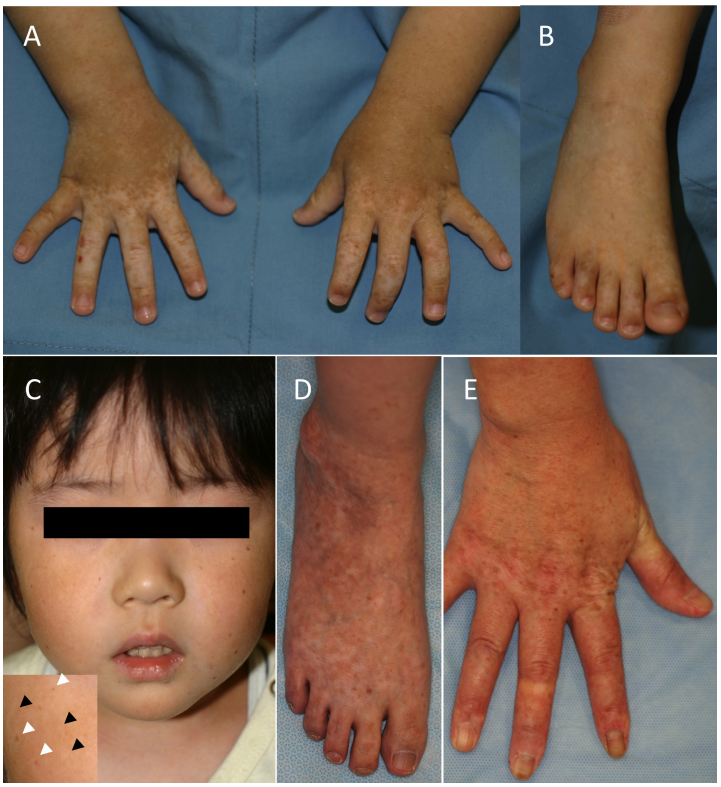

Fig. 2 Representative clinical features of DSH patients in the present study
(A–C) Case 3: A mixture of hyperpigmented and hypopigmented macules are seen on the dorsal aspects of the hands (A) and the foot (B). In addition, a few small, scattered, discrete "freckle-like" pigmented macules with hypopigmented macules are seen (C). Pigmented macules (open arrowheads) and hypopigmented macules (closed arrowheads) are indicated in the inset of C. (D, E) Case 4: Similar skin manifestations are observed on the dorsal aspects of the foot (D) and the hand (E) of an adult patient.

the data of each proband in those families, except for Family B in Table 1. The detained clinical features of each case are described here (Fig. 2).

Case 1 (Family A)

A 43-year-old man presented with small hyper- and hypo-pigmented macules on the extremities, including the upper arms and the thighs, and on the neck. He had a small number of small, brown freckle-like macules, and the skin lesions even spread on his face and groin. He had been suffering from these symptoms since about the age of 6. According to the proband, his father had similar symptoms. However, we have not included his data in our evaluation, because detailed information with which to evaluate his skin manifestations could not be obtained. Skin biopsy specimens from the hyper- and hypopigmented macules on the dorsa of the hands showed the hypopigmented lesions to have less melanin pigment in the basal layer of the epidermis than the hyperpigmented lesions had, although melanocytes were recognized in both lesions. In the hyperpigmented lesions, a few thick dendrites of melanocytes were seen in the epidermis.

Case 2 (Family B)

A 5-year-old girl presented with indistinct small hyper- and hypo-pigmented macules on the dorsa of the hands and feet, the forearms, the lower legs and the thighs. In addition, she had freckle-like brown macules on the cheeks. Her father had similar small hyper- and hypo-pigmented macules on the extremities, including the upper arms and the thighs, and on the shoulder and neck. He also had freckle-like brown macules on the face. Neither the proband nor her father showed depigmentation on the face.

Case 3 (Family C)

The patient was a 2-year-old boy who had been born with no complications. 1 year after his birth, small hyper- and hypo-pigmented spots appeared on the dorsal aspect of the hands and feet. Subsequently, these macules extended to the upper arms and thighs. He had a mixture of hyper- and hypo-pigmented spots on the cheeks. His father had similar symptoms, but detailed information of his skin manifestations with which to evaluate the severity of those lesions was not provided.

Case 4 (Family D)

A 34-year-old woman presented with pigmented spots of 2–7 mm in diameter, which scattered within reticular hypopigmented macules on the dorsal aspect of the hands and feet. Subsequently, the macules spread to the forearms and lower legs. The lesions were irregular in size and shape. She had freckle-like pigmented macules and a few depigmented macules on the face. She had been suffering from this symptom since her neonatal period. The skin symptoms gradually became prominent. She had no noteworthy family history. She also had autoimmune hemolytic anemia.

Case 5 (Family E)

A 36-year-old woman presented with reticular hyper- and hypo-pigmented macules on all the extremities, including the nape. She also had freckle-like pigmented macules and a few depigmented macules on the face. She had been suffering from these symptoms since around the age of 4 years. The skin lesions had gradually worsened with age. Her mother and her 5-year-old son had similar symptoms, although the detailed information of their skin manifestations was not obtained for severity grading.

Evaluation of DSH Disease Severity

To investigate correlations between genotypes and the severity of the skin manifestations or the presence/absence of other clinical symptoms, we defined the severities of skin manifestations on the extremities as follows: mild, the lesions are restricted to the dorsa of the hands or feet; moderate, the lesions extend to the forearms or the lower legs; severe, the lesions extend beyond the elbow or the knee.

Mutation Detection

The Ethics Committee and the institutional review board of Nagoya University Graduate School of Medicine approved the present study. All experiments and analyses were conducted in accordance with the Declaration of Helsinki Principles. We obtained fully-informed, written consent from all the patients or from the patient's legal guardians.

We extracted genomic DNA from peripheral blood samples using the QIAamp DNA Blood Maxi Kit (Qiagen, Valencia, CA). In this study, standard PCR amplification procedures were employed, with high-fidelity polymerase, Platinum Taq DNA Polymerase (Invitrogen, Carlsbad, CA, USA) and 37.5 ng genomic DNA as the template in 50-μL volume. The thermal conditions

were the following: 94 ºC for 5 min, followed by 30 cycles at 94 ºC for 15 s, 60 ºC for 30 s and 72 ºC for 1 min, with final extension at 72 ºC for 10 min. The set of amplified PCR fragments with each primer is shown in a previous report.[13] PCR products were purified by QIAquick PCR Purification Kit (Qiagen) and sequenced directly with the same primers as used for each PCR amplification to identify mutations by Sanger sequencing with Applied Biosystems 3730 DNA Analyzer.

RESULTS

Mutations Detected in the Present DSH Cases and Their Consequences

ADAR1 mutations detected in the present DSH cases and their consequences are summarized in Table 1 and Fig. 3.

Case 1. The heterozygous nonsense mutation p.Cys893X (c.2679T>A) in exon 9 is located in the adenosine deaminase domain (Fig. 3) and leads to premature translation termination (PTC). Truncated proteins without functional activity are expected to be synthesized, or nonsense-mediated mRNA decay (NMD) is expected to occur and RNA with the mutation degrades. These phenomena result in *ADAR1* haploinsufficiency. Generally, a PTC can initiate NMD as long as the stop codons are more than 50–55 nucleotides upstream of the 3'-most splice site.[14] This mutation was previously found in another Japanese DSH family.[6]

Case 2. The previously reported heterozygous p.Arg1096X (c.3286C>T) nonsense mutation[15-20] was identified in exon 13 of *ADAR1* (Fig. 3). The predicted protein lacks 131 amino acids, which are part of the adenosine deaminase domains, just as Case 1 lacks them.

Case 3. The heterozygous nonsense mutation p.Arg474X (c.1420C>T) in exon 2 of *ADAR1*, which was previously reported in 3 Chinese[17,18,21] and in 1 Japanese[8] family with DSH, was identified (Fig. 3). The mutation generates a translational termination codon.

Case 4. The heterozygous missense mutation p.Arg916Trp (c.2746C>T) was identified in exon 9, which is in a highly conserved region of the deaminase domain (Fig. 3). This mutation was previously reported in a Chinese family[22], but we found this mutation in a sporadic case.

Case 5. A p.Gly471Aspfs*30 (c.1601G >A) at the end of exon 2 of *ADAR1* was previously reported in a Chinese family (Fig. 3).[23] In the report, this mutation was proved to activate the cryptic splicing donor site GT lying upstream of the normal splicing donor site in exon 2 and thus the mutation causes a 190-bp deletion in the mRNA sequence by the functional loss of the native intron 2 donor site. This deletion causes a reading frame shift from codon 471 with 29 aberrant amino acids and generates premature termination at codon 500.

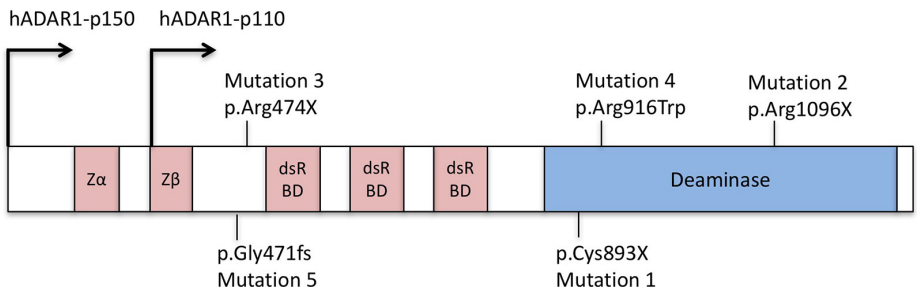

Fig. 3 The scheme of the domain structure of ADAR1 and five mutations detected in the present study ADAR1 p150 has two Z-DNA binding domains (Z-DBDs), Zα and Zβ; three double-stranded RNA binding domains (dsRBDs); and a deaminase domain.

Analysis of the Clinical Features of the Present DSH Cases and a Review of the Literature for Cases with Identical Mutations

Mutation 1: c.2679T>A (p.Cys893*) in Case 1. Only two families (three patients) with this mutation have been reported, including the present Case 1. Hypopigmented macules on the face were seen in only one previously reported patient, while freckle-like macules on the face were seen in that case and the present Case 1.

Mutation 2: c.3286C>T (p.Arg1096*) in Case 2. Seven unrelated families with this mutation were reported previously in six articles. As eight unrelated families, including the present Family B, have been reported, this mutation is relatively common. It could be a founder mutation. The symptoms on the extremities varied from mild to severe. In 45.5% of the cases with p.Arg1096*, hyperpigmented lesions on the face were shown, but there were no cases with hypopigmented lesions on the face. In contrast, 93.8% of the cases with the 4 other mutations in the present study showed hyperpigmented lesions on the face. p.Arg1096* had a significant inverse correlation with freckle-like macules on the face (odds ratio = 0.056 [95% CI: 0.007–0.47, p = 0.0011]). Thus, this mutation is thought to be associated with the absence of freckle-like macules on the face.

Mutation 3: c.1420C>T (p.Arg474*) in Case 3. As far as we know, all cases with this mutation were reported to have freckle-like macules on the face, with skin manifestations on the extremities of various severities. A previously reported Chinese patient with p.Arg474* and the present Case 3 had hypopigmentation on the face, which was shown in only these two cases out of the total 49 cases, in whom severity of facial lesions was evaluated in the present study. As this mutation was reported in 5 unrelated families, including the present Family C, it could be regarded as common and as a founder mutation.

Mutation 4: c.2746C>T (p.Arg916Trp) in Case 4. In comparison with the previous case with the identical mutation c.2746C>T, it might be worth mentioning that the present Case 4 has shown symptoms since birth and that she has autoimmune hemolytic anemia. These present and previous cases with the identical mutation c.2746C>T were consistent in the severity of the skin manifestation on extremities as moderate.

Mutation 5: c.1601G>A (p.Gly471Aspfs*30) in Case 5. In terms of clinical features, all cases with this mutation showed freckle-like macules on the face but the skin manifestations on the extremities were of varying severities.

Clinical features for each mutation. We investigated the clinical features of the DSH patients with the present five mutations. We were unable to find any differences in the severity of the skin manifestations on the extremities among the patients with these five mutations. Regarding Mutation 2, as we mentioned above, we confirmed statistically freckle-like macules on the face to be less frequent among the patients harboring Mutation 2 than among those harboring the four other mutations. Regarding Mutation 4, the present Case 4 showed the skin manifestations at birth and had autoimmune hemolytic anemia as a complication. Of the patients with the five mutations described in the present study, only Case 4, who had Mutation 4, had skin manifestations at birth and extracutaneous complications.

Analysis of Correlations between the Severity of Lesions on the Extremities, and Other Clinical Features

We evaluated the severity of the typical skin symptoms on the extremities in the present DSH patients and DSH patients with identical ADAR1 mutations reported in the literature. The results are also summarized in Table 1.

We investigated correlations between the presence/absence of skin manifestations on the face and the severity of skin lesions on the extremities. Presence or absence was evaluated in the present DSH cases and in previously reported DSH cases, for a total of 29 patients. Of these

29 patients, 21 patients had facial lesions. Of the 21 patients with facial lesions, 10 patients had skin manifestations of more than moderate grade in the extremities, and 11 patients had skin lesions of mild grade on the extremities. All 8 patients without facial lesions had skin symptoms of mild grade in the extremities. The presence of facial lesions was associated with greater severity of lesions on the extremities (odds ratio = 15.2 [95% CI: 0.7939–303.5, p = 0.0265]).

Focusing on hypopigmentation in the facial lesions, presence or absence was evaluated in the 29 patients. Of the 29 patients whom we were able to evaluate for both hypopigmentation and the severity of skin lesions on the extremities, four patients had hypopigmentation in facial lesions. Of these 4, one patient showed mild lesions on the extremities and the other three patients showed lesions on the extremities of more than moderate grade. We were unable to include a patient with hypopigmentation on the face in the Chinese family with Mutation 3 that was reported by Sun *et al.*21), because we were unable to obtain the information on the severity of skin manifestations on the extremities. In contrast, of the 25 patients without hypopigmentation of the face, 18 patients showed mild lesions on the extremities and 7 patients showed the lesions on the extremities of more than moderate grade. Thus, we investigated whether the hypopigmentation on the face was associated with severe skin manifestations on the extremities. Hypopigmentation on the face was found to be non-significantly associated with the severity of skin manifestations on the extremities (odds ratio = 7.71 [95% CI: 0.677–48.0, p = 0.1048]).

DISCUSSION

The *ADAR1* protein is composed of two adenosine deaminase Z-alpha domains, three double-stranded (ds) RNA-binding domains and a dsRNA adenosine deaminase domain, and these are encoded by exons 2, 2–7 and 9–15 of ADAR1, respectively.[24] The protein catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates, resulting in the creation of alternative splicing sites or codon alternations that lead to functional changes in the protein.[25] ADAR1 is expressed ubiquitously and is assumed to be a housekeeping gene.[26]

Here we detected five previously described *ADAR1* mutations in four Japanese families and one sporadic patient of Japanese origin with DSH. In the present study, we analyzed the clinical features in all families and previously reported cases with each mutation detected in the present study. In addition, we analyzed correlations between the clinical features and the mutation sites of *ADAR1* gene in the cases to elucidate the characteristic clinical features that depend on the mutation sites of the gene. Regarding the mutations c.3286C>T (Mutation 2) and c.1420C>T (Mutation 3), there were multiple families with the mutations in the Japanese and Chinese populations. From this fact, we speculate that they might be common founder mutations.

We also evaluated the severity of skin symptoms in our patients and in the previous reported DSH patients and summarized these in Table 1.

No significant difference was found in the severity of the skin lesions between the upper extremities and the lower extremities. The dorsal hand is a sun-exposed part, and the dorsal foot is a non-exposed part. The absence of a significant difference in severity between them may suggest that sun exposure does not affect the formation of the skin manifestations. A recently reported study showed that sun exposure is just a transiently aggravating factor.[27] Our present findings support the conclusion of the report. The skin manifestations on the hands of DSH patients were known to be tend to exacerbate in summer.

The frequency of facial lesions in the patients with the mutation c.3286C>T was significantly lower than the frequency of facial lesions in the patients with the other 4 *ADAR1* mutations, i.e. less than half of the patients with the mutation c.3286C>T had facial lesions. On this point,

although previous reports[18,28] mentioned that there are no genotype-phenotype correlations in DSH with *ADAR1* mutations, there might be a certain phenotype-genotype correlations in the frequency of facial lesions.

It has been thought that an identical mutation can lead to different phenotypic severities even in the same family, and no clear correlations between genotypes and phenotypes have been established. In the present study, we objectively evaluated the severity of skin manifestations using our definition of severity levels. This is the first semi-quantitative evaluation of skin manifestations of DSH. From our analysis under our definition of severities, patients who had freckle-like facial lesions significantly have more severe symptoms on the extremities. Patients whose freckle-like facial lesions were accompanied by hypopigmented macules tended to have more severe symptoms on the extremities. In addition, we found a novel phenotype-genotype correlation between the presence/absence of facial lesions and the *ADAR1* mutation c.3286C>T. The mutation c.3286C>T was significantly associated with the absence of freckle-like macules on the face, compared with the other 4 *ADAR1* mutations (odds ratio = 0.056 [95% CI: 0.007–0.47, $p < 0.005$]).

We agree that the overall phenotype of DSH cannot be explained by genotype alone and that some factors, such as viral infection *in utero* and/or in infancy, may affect the phenotypic expression.[3,28] However, to understand the pathogenesis of DSH completely, we should develop a way of elucidating such disease-modifying factors for DSH.

CONFLICTS OF INTEREST

The authors declare that we have no conflicts of interest.

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