Mutation Analysis of the *ADAR1* Gene in Dyschromatosis Symmetrica Hereditaria and Genetic Differentiation from both Dyschromatosis Universalis Hereditaria and Acropigmentatio Reticularis

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Dyschromatosis symmetrica hereditaria (DSH) (also called ''reticulate acropigmentation of Dohi'') is a pigmentary genodermatosis of autosomal dominant inheritance. We have clarified for the first time four pathological mutations of the double-stranded RNA-specific adenosine deaminase gene (*ADAR1 or DSRAD*) in four DSH pedigrees. In this paper, we report 16 novel mutations containing six missense substitutions (p.V906F, p.K1003R, p.G1007R, p.C1036S, p.S1064F, p.R1078C), two splice site mutations (IVS2 + 2T > G, IVS8 + 2T > A), six frameshift mutations (p.H216fs, p.K433fs, p.G507fs, p.P727fs, p.V955fs, p.K1201fs), and two nonsense mutations (p.R426X, p.Q600X) found in Japanese patients with DSH. We did not establish any clear correlation between the clinical phenotypes and the genotypes of *ADAR1* gene mutations in our examination of 16 cases plus four pedigrees. None of the different mutations identified in our studies of 20 cases suggested any founder effect. Furthermore, we did not identify any mutations in the *ADAR1* gene of three patients with dyschromatosis universalis hereditaria or three patients with acropigmentatio reticularis, indicating that the two diseases are completely different from DSH, although they have sometimes been suggested to be phenotypical variations of DSH.

Key words: adenosine deaminase/DSRAD/Japanese/pigmentation disorders/RNA editing
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Dyschromatosis symmetrica hereditaria (DSH [MIM127400]) (also called "reticulate acropigmentation of Dohi") is an autosomal dominant disease characterized by a mixture of hyperpigmented and hypopigmented macules distributed on the dorsal aspects of the extremities and freckle-like macules on the face (Toyama, 1910, 1929) (Fig 1*A* and *B*). DSH has been reported mainly in Japan, although a few cases were described among Koreans, Indians, Chinese, Europeans, and South Americans (Oyama *et al*, 1999). Recently, 17 DSH families including 136 cases in China were reported (He *et al*, 2004), indicating that this disorder might be distributed mainly in East Asia. The difference in the frequency of this disorder between East Asia and other regions may be related to genetic background and/or environment, e.g., the amount of UV exposure. From the results of linkage analysis and a genome-wide scan, we have for the first time clarified that a heterozygous mutation of the RNA-specific adenosine deaminase gene (*ADAR1*, *DSRAD*) causes DSH, and have also reported four heterozygous mutations of p.R474X, p.L923P, p.K952X, and p.F1165S in the *ADAR1* gene responsible for DSH in Japanese families (Miyamura *et al*, 2003). Subsequently, two groups reported two and eight novel mutations in the *ADAR1* gene in Chinese patients with DSH, respectively (Li *et al*, 2004; Liu *et al*, 2004; Zhang *et al*, 2004), which confirmed that the *ADAR1* gene is responsible for DSH not only in Japanese but also in another ethnic groups.

ADAR1 was identified as the first enzyme that converts adenosine to inosine in double-stranded RNA (Bass and Weintraub, 1988). Inosine acts as guanosine during translation and reverse-transcription. It appears to be the most widespread type of nuclear pre-mRNA editing in higher eukaryotes. RNA editing reactions occur in many organisms and operate by different molecular mechanisms. In some

Abbreviations: ADAR, adenosine deaminase acting on RNA; AR, acropigmentatio reticularis; DSH, dyschromatosis symmetrica hereditaria; DSRAD, double-stranded RNA-specific adenosine deaminase; DUH, dyschromatosis universalis hereditaria; SSCP/HD, single-strand conformation polymorphism/heteroduplex

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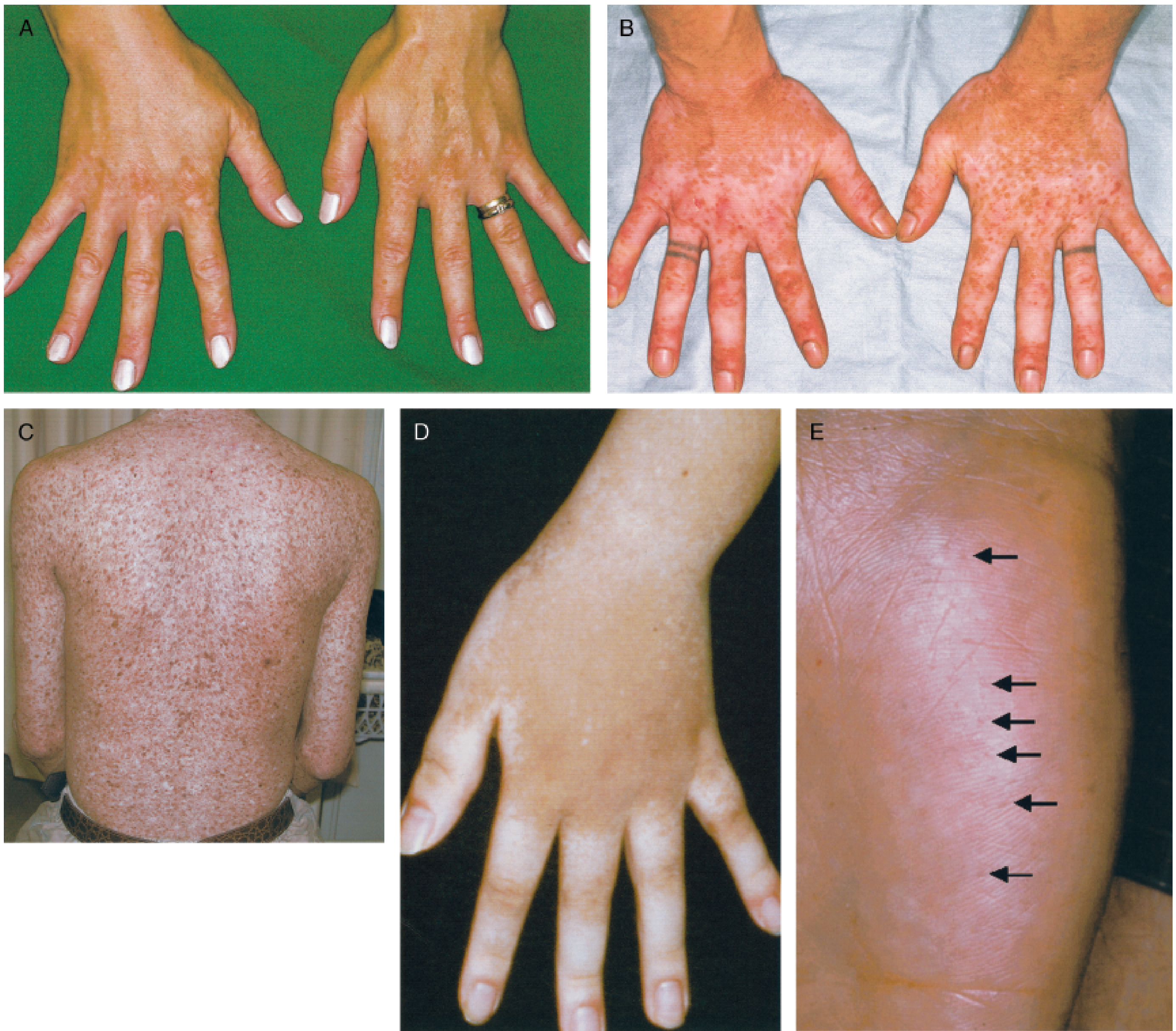

Figure 1
Clinical phenotypes of dyschromatosis symmetrica hereditaria (DSH), dyschromatosis universalis hereditaria (DUH), and acropigmentatio reticularis (AR). (*A*) Patient 3 with DSH, (*B*) patient 8 with DSH. The mixtures of hyper- and hypopigmented macules on the dorsal aspects of hands were various. The phenotype in patient 3 was faint and less severe than that in patient 8. (*C*) DUH. Mixtures of hyper- and hypopigmented macules occur all over the body. (*D*), (*E*) AR. Hyperpigmented macules distributed on the dorsal aspects of the hands and feet with no hypopigmented ones. "Pits" on the palms (*arrows*) were observed.

substrates, the editing occurs at specific sites to produce codon changes within open reading frames, whereas in others an alternative splice acceptor site is created, or modulation of mRNA stability or transport is changed by editing pre-mRNA (Maas *et al*, 2003). Loss of those functions might cause the phenotypes of DSH, although the mechanisms still remain unknown.

There are two diseases showing phenotypes so similar to DSH that they are sometimes difficult to differentiate from DSH. One of them is dyschromatosis universalis hereditaria (DUH [MIM127500]), initially described by Ichikawa and Hiraga (1933). In DUH, mixtures of hyperpigmented and hypopigmented macules occur all over the body (Fig 1*C*). By the localization of the skin lesions, the disease can be discriminated from DSH. And DUH has been thought to be distinct from DSH because they have not been found together in the same pedigree. We previously suggested (Miyamura *et al*, 2003) that DUH might have been the diagnosis in the two families in which Xing *et al* (2003) found linkage to 6q24.2–q25.2. The other disease is acropigmentatio reticularis (AR) (Kitamura *et al*, 1953), also called "reticulate acropigmentation of Kitamura" (Griffiths, 1976), which is also an autosomal dominant disease characterized by reticulate, hyperpigmented macules distributed on the dorsal aspects of the hand and feet, "pits" on the palms, and the absence of hypopigmented macules (Fig 1*D* and *E*). It is controversial whether AR is a variant of DSH. So far there has been no report on the chromosomal location or etiology of AR.

In this paper, we report 16 novel mutations in Japanese patients with DSH; these mutations help to define a func-

tionally important region in the deaminase domain. We also report that none of the three patients with DUH or the three patients with AR had any mutations in the *ADAR1* gene, supporting the notion that DSH is a distinct disease from DUH or AR. This is a report showing molecular evidence of the differences between DSH and DUH as well as AR.

Results and Discussion

Mutations of the *ADAR1* gene in patients with DSH PCR-single-strand conformation polymorphism/heteroduplex (SSCP/HD) screening and direct sequencing of the 16 patients with DSH revealed 16 novel mutations of the *ADAR1* gene (Table I). The 16 novel mutations included six missense substitutions (p.V906F, p.K1003R, p.G1007R, p.C1036S, p.S1064F, p.R1078C), two splice site mutations (IVS2+2T>G, IVS8+2T>A), six frameshift mutations (p.H216fs, p.K433fs, p.G507fs, p.P727fs, p.V955fs, p.K1201fs), and two nonsense mutations (p.R426X, p.Q600X). We examined the frequency of the six missense and the two splice site mutant alleles in the *ADAR1* gene of 114 unrelated normally pigmented Japanese subjects (228 alleles), and no mutant allele was detected. This suggested that those 8 alleles were very rare in the normal Japanese population and could be defined statistically as pathological alleles. Furthermore, in the case of a splice site mutation, IVS8+2T>A, we confirmed an aberrant splice product with RT-PCR and DNA direct sequence analysis. The result revealed that exon 8 was spliced to exon 9 with the presence of the first 80 nucleotides from intron 8, resulting in a frameshift and a truncated protein with an additional 2-amino-acid peptide. In another splice site mutation, IVS2+2T>G, we predicted that the T>G change at the second base of IVS2 might cause a similar aberrant splicing. We could not, however, obtain experimental evidence because the patient did not agree to provide an additional blood sample for the RT-PCR work. All of the six novel missense mutations identified in this study and another five missense mutations described previously (Miyamura *et al*, 2003; Li *et al*, 2004; Liu *et al*, 2004; Zhang *et al*, 2004) were

Table I. Mutations of the *ADAR1* gene in this study

Patient	Disease	Incidence	Affected individuals	Unaffected individuals	Nucleotide change[a]	Amino acid change	Exon	Mutation type
1	DSH	Familial	3	1	c.645–646insCC	p.H216fsX261	EX2	Frameshift
2	DSH	Familial	4	9	c.1276A>T	p.R426X	EX2	Nonsense
					c.1826T>C	p.F609S	EX4	Missense
3	DSH	Familial	5	11	c.1296–1297insTG	p.K433fsX433	EX2	Frameshift
4	DSH	Familial	7	5	c.1521delG	p.G507fsX509	EX2	Frameshift
5	DSH	Familial	6	9	IVS2+2T>G	Unknown	IVS2	Splice mutation
6	DSH	Familial	5	2	c.1798C>T	p.Q600X	EX4	Nonsense
7	DSH	Familial	4	15	c.2180delC	p.P727fsX792	EX6	Frameshift
8	DSH	Familial	7	13	IVS8+2T>A	p.G890fsX892	IVS8	Splice mutation
9	DSH	Sporadic	—	—	c.2716G>T	p.V906F	EX9	Missense
10	DSH	Familial	2	6	c.2865–2866delGT	p.V955fsX972	EX10	Frameshift
11	DSH	Familial	7	5	c.3008A>G	p.K1003R	EX11	Missense
12	DSH	Familial	2	10	c.3019G>A	p.G1007R	EX11	Missense
13	DSH	Sporadic	—	—	c.3107G>C	p.C1036S	EX12	Missense
					c.1752–1754delATC	p.S585del	EX3	Frameshift
14	DSH	Familial	3	10	c.3191C>T	p.S1064F	EX12	Missense
15	DSH	Familial	5	3	c.3232C>T	p.R1078C	EX13	Missense
16	DSH	Familial	8	9	c.3603delA	p.K1201fsX1203	EX15	Frameshift
17	DUH	Familial	4	6	None	None		
18	DUH	Sporadic	—	—	None	None		
19	DUH	Sporadic	—	—	None	None		
20	AR	Familial	2	1	None	None		
21	AR	Familial	4	4	None	None		
22	AR	Sporadic	—	—	None	None		

[a]GenBank Accession No. NM_001111. Position 1 is A of the translation initiation codon.
DSH, dyschromatosis symmetrica hereditica.

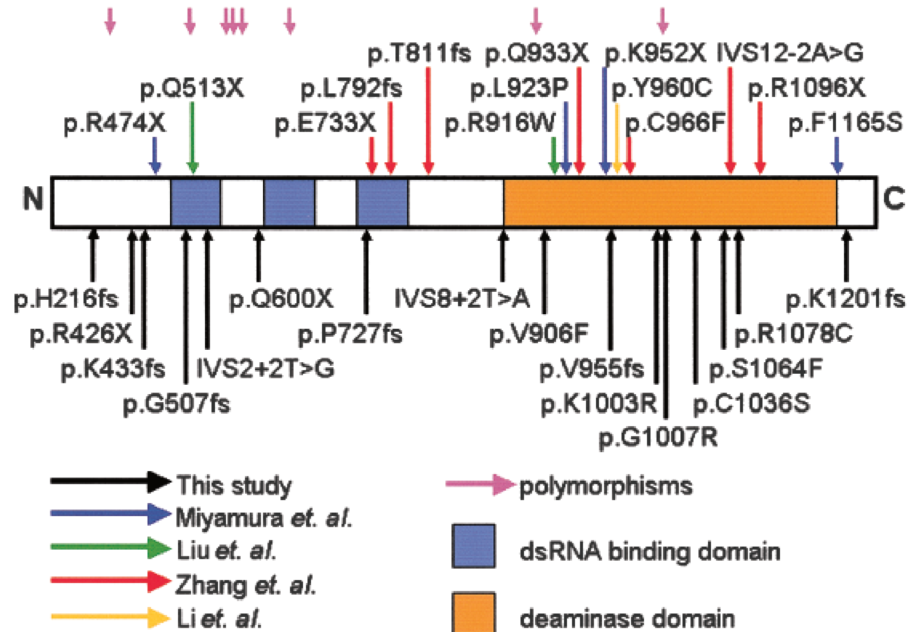

Figure 2
Mutations of the *ADAR1* gene found in patients with dyschromatosis symmetrica hereditaria. The new mutations and polymorphisms identified in this study are indicated by black and pink arrows, respectively. Blue, green, red, and yellow arrows indicate mutations reported previously. N, N-terminal; C, C-terminal.

located at amino-acid residues conserved among the zebrafish, frog, chicken, mouse, and human within the deaminase domain of the ADAR1 protein (Fig 2). These results suggested that the mutations play an important role in the confirmation of the catalytic site of the enzyme and likely influence the deaminase activity.

Patient 2 turned out to have two mutations, p.R426X and p.F609S (Table I). We examined the frequency of these two mutations among 101 of the normally pigmented Japanese subjects (202 alleles), and neither mutation was detected. Further analysis of his father with DSH showed that he also had both mutations, indicating that the two mutations must be certainly on the same allele derived from him, but not on two heterozygous alleles. Therefore, the p.F609S mutation might not give any influence in this patient because of the existence of the previous p.R426X mutation, which would lead to premature translation resulting in a truncated protein with no functional activity. And this would not be contradictory to a report that homozygosity for the *Adar1* null mutation would cause embryonic lethality in mice (Wang *et al*, 2004).

Identification of polymorphisms We identified six novel polymorphisms in the exonic or the nearby intronic sequences in the *ADAR1* gene, and the frequencies were determined for 16 patients with DSH and 113 unrelated normal Japanese subjects (Table II). Two of the exonic polymorphisms resulted in amino-acid changes (p.K384R, p.Y587C), one resulted in an in-frame mutation (p.S585del), whereas the remaining ones were silent. A three-base deletion (ATC) at c.1752–1754, which was an in-frame mutation resulting in a deletion of serine located outside of the deaminase domain, was found in one patient (patient 13) and two normally pigmented Japanese. Patient 13 was homozygous for this deletion and heterozygous for p.C1036S (Table II). The amino-acid substitution from cystein to serine at codon 1036 is a non-conserved change located within the deaminase domain, suggesting a pathological mutation. And the two normal subjects who were heterozygous for p.S585del mutant allele had no evidence for DSH. Based on these data, we concluded that the deletion of the serine codon 585 is a sequence polymorphism rather than a pathogenic mutation, although the possibility of a rare recessive allele cannot be excluded.

The relationship between the phenotype and the mutant genotype in the *ADAR1* gene We compared the clinical features among the patients with the mutations identified in the 16 cases. All of the patients had a mixture of hyper- and hypopigmented macules to various extents, which first appeared in infancy or early childhood. Some patients (e.g., patient 8, Fig 1*B*) had markedly clear macules. On the other hand, faint macules were found on the dorsal aspects of the extremities of the other patients (e.g., patient 3, Fig 1*A*). We failed, however, to find any relationship between the phenotypes and genotypes; even in the same family and pedigree among those who had the same mutation, the pattern and the degree of the skin lesions were various. There was no tendency that the phenotype in a patient who had a missense mutation or a relatively long truncation peptide might be less severe than that in a patient with an early truncation mutation. These data indicated that the phenotypes might be influenced not only by mutant genotypes in the *ADAR1* gene but also by other genes or, possibly, the patient's environment, e.g., repeated exposure to UV light on the dorsal aspects of the hands and feet.

DUH and AR We screened mutations in the *ADAR1* gene in the three patients with DUH and three patients with AR by both the SSCP/HD method and direct sequencing of all their PCR products. No mutation, however, was identified (Table I). These findings indicated that the gene causing DUH or AR should be different from *ADAR1* and that these disorders are genetically and etiologically distinct from DSH. And they also supported our previous suggestion that DSH and DUH may be two distinct diseases, that is, the

Table II. Polymorphisms detected in the *ADAR1* gene and its frequencies in Japanese patients with DSH and normally pigmented Japanese subjects

Nucleotide change	Amino acid change	Exon	Allele frequency in: Japanese patients with DSH	Allele frequency in: Normally pigmented Japanese subjects
c.1151G>A	p.R384K	EX2	7/24(0.29)	10/36(0.28)
c.1410A>G[a]	p.P470P (silent)	EX2	0/32(0.00)	1/36(0.03)
c.1752–1754delATC[a]	p.S585del	EX3	2/32(0.06)	2/226(0.01)
c.1760A>G[a]	p.Y587C	EX3	0/32(0.00)	2/226(0.01)
IVS3+5G>A[a]	None	IVS3	0/32(0.00)	4/226(0.02)
IVS4-20C>T[a]	None	IVS4	1/32(0.03)	1/36(0.03)
c.2682G>A	p.V894V (silent)	EX9	7/20(0.35)	64/222(0.29)
IVS11+9T>C[a]	None	IVS11	0/32(0.00)	1/36(0.03)

[a]Novel polymorphism.
DSH, dyschromatosis symmetrica hereditaria.

locus for DUH might link to chromosome 6q24.2–q25.2 whereas that for DSH links to chromosome 1q21.3 (Miyamura *et al*, 2003).

Recently, Nuber *et al* (2004) reported in an ultrastructural skin investigation of DUH patients that DUH might not be a disorder of the melanocyte number, but rather that of the melanosome synthesis rate. This is intriguing in view of reports describing that the pigment anomaly in DSH might be due to the small number of melanocytes (Hata and Yokomi, 1985), indicating that the two diseases might be caused by quite different mechanism(s) in spite of the similarity in phenotypes.

AR had sometimes been proposed to be a variant of DSH. Hyperpigmented macules, which are similar to those of DSH, distribute on the dorsal aspects of the hands and feet. The difference in clinical features from DSH is the absence of hypopigmented macules (Fig 1*D*), which are always found in DSH. "Pits" on the palms (*arrows*) are observed in AR and enable one to differentiate between DSH and AR (Fig 1*E*). Our present data indicated that AR is an entirely different disease from DSH.

ADAR1 protein is composed of 1226 amino acid residues, with a calculated molecular mass of 139 kDa (O'Connell *et al*, 1995). It catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates (Bass and Weintraub, 1988; Wagner *et al*, 1989), which results in the creation of alternative splicing sites (Rueter *et al*, 1999) or alternations of codon and thus leads to functional changes in proteins. The *ADAR1* gene is expressed ubiquitously (Kim *et al*, 1994), but a few known target genes for ADAR1 are expressed in specific tissues, e.g., ionotropic glutamate receptor (Higuchi *et al*, 1993; Lomeli *et al*, 1994) and the serotonin receptor 2C subtype in the brain (Burns *et al*, 1997), and hepatitis delta virus antigen in the liver (Polson *et al*, 1996). And it was also reported that the *ADAR1* expression was increased in the spleen, thymus, and peripheral lymphocytes of endotoxin-treated mice (Yang *et al*, 2003). The target genes and the induction of the enzyme in lymphocytes, however, are unlikely to be involved in the pathogenesis of DSH. Wang *et al* recently reported that homozygosity for the *Adar1* knockout in mice caused embryonic lethality, indicating that *Adar1* was essential for life. And they further observed that fibroblasts derived from $Adar^{-/-}$ embryo were prone to apoptosis induced by serum deprivation. $Adar^{+/-}$ heterozygous mice, however, exhibited no obvious abnormalities such as skin lesions (Wang *et al*, 2004). The absence of skin lesions in the heterozygous mice may depend on differences between the two splices.

The mechanism by which mutations in *ADAR1* gene cause DSH still remains unknown. We speculate two hypotheses as follows. The first is that, when melanoblasts migrate from the neural crest to the skin during development, a greater reduction in ADAR1 activity might occur at anatomic sites distant from the neural crest. The failure of correct RNA editing may induce the differentiation of melanoblasts to hyperactive or hypoactive melanocytes, which then colonize in an irregular distribution resulting in skin lesions. The second hypothesis is that the ADAR1 activity is required for protection against stress-induced apoptosis as mentioned above (Wang *et al*, 2004). Accordingly, a greater reduction in ADAR1 activity would cause apoptosis in melanocytes at sites exposed to UV light and would result in hypopigmented macules on the back of the hands and the top of the feet. And secondarily, hyperpigmentation might occur around hypopigmented macules completing the mixture of hypo- and hyperpigmented macules. These hypotheses were based on the idea that nonsense-mediated RNA decay would occur and DSH might be caused by haploinsufficiency of the ADAR1 activity, because we failed to identify a clear relationship between the phenotypes and genotypes in this study described above. That is, there was no phenotypical difference in terms of the kind and site of the mutations. A dominant negative effect of mutant ADAR1 activity, however, could also be proposed as a mechanism as well as haploinsufficiency. Recently, homodimerization was demonstrated to be essential for the enzyme activity of the *ADAR1* encoded protein (Cho *et al*, 2003). Both the double-stranded RNA binding motif and deaminase domain were suggested to be required for the

formation of the homodimer (Cho *et al*, 2003), suggesting that DSH might be caused by a dominant negative effect (Liu *et al*, 2004). Further investigations will be needed to address this issue.

In conclusion, in this study, 16 novel mutations in the *ADAR1* gene were found in 16 Japanese patients with DSH, suggesting no founder effect in DSH patients. And this study also established the existence of apparent differences in the etiology of DSH, DUH, and AR. Identification of the genes for DUH and AR is expected.

Materials and Methods

Patients All patients were Japanese and unrelated. A total of 16 patients with DSH, three patients with DUH, and three patients with AR were included in the mutational analysis. Two, two, and one of the patients with DSH, DUH, and AR, respectively, had no family history of the disease and the families of the other patients turned out to have at least one other affected individual in each family (Table II). We screened one affected individual of each pedigree for a mutation of the *ADAR1* gene. The birthplaces of the patients were scattered around Japan, and no high incidence area for these three diseases were found. The patients originally consulted us for their skin conditions. The degree of hyper- and hypopigmentation in each patient varied from distinct to indistinct. This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine. This study was conducted according to the Declaration of Helsinki Principles. Informed written consent was obtained from each patient, or from the patient's parents in the case of children.

Mutation screening and detection Mutation analysis of the *ADAR1* gene was performed as previously described (Miyamura *et al*, 2003). Briefly, genomic DNA was extracted from peripheral blood leucocytes and used as a template for mutational screening using a PCR-based SSCP/HD analysis (Spritz *et al*, 1992). Standard PCR amplification procedures were employed, with an annealing temperature of 62°C for all primers (see Table S1). Three kinds of SSCP gels, with glycerol concentrations of 0%, 7%, and 10%, were used to elevate the sensitivity of our mutation screening system. PCR products showing aberrant patterns on SSCP were reamplified and sequenced directly to identify the mutation. In patients without any mutations detected by the SSCP/HD method, all of their PCR products were directly sequenced to identify any mutations.

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Supplementary Material

The following material is available from http://www.blackwellpublishing.com/products/journals/suppmat/JID/JID23732/JID23732.htm
Table S1. Primer pairs used to amplify the *ADAR1* gene exon segments.

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References

Bass BL, Weintraub H: An unwinding activity that covalently modifies its double-stranded RNA substrate. Cell 55:1089–1098, 1988

Burns CM, Chu H, Rueter SM, Hutchinson LK, Canton H, Sanders-Bush E, Emeson RB: Regulation of serotonin-2C receptor G-protein coupling by RNA editing. Nature 387:303–308, 1997

Cho DS, Yang W, Lee JT, Shiekhattar R, Murray JM, Nishikura K: Requirement of dimerization for RNA editing activity of adenosine deaminase acting on RNA. J Biol Chem 278:17093–17102, 2003

Griffiths WA: Reticulate acropigmentation of Kitamura. Br J Dermatol 95: 437–443, 1976

Hata S and Yokomi I: Density of dopa-positive melanocytes in dyschromatosis symmetrica hereditaria. Dermatologica 171:27–29, 1985

He PP, He CD, Cui Y, *et al*: Refined localization of dyschromatosis symmetrica hereditaria gene to a 9.4-cM region at 1q21–22 and a literature review of 136 cases reported in China. Br J Dermatol 150:633–639, 2004

Higuchi M, Single FN, Kohler M, Sommer B, Sprengel R, Seeburg PH: RNA editing of AMPA receptor subunit GluR-B: A base-paired intron exon structure determines position and efficiency. Cell 75:1361–1370, 1993

Ichikawa T, Hiraga Y: A previously undescribed anomaly of pigmentation dyschromatosis universalis hereditaria. Jpn J Dermatol Urol 34:360–364, 1933 (in Japanese)

Kim U, Wang Y, Sanford T, Zeng Y, Nishikura K: Molecular cloning of cDNA for double-stranded RNA adenosine deaminase, a candidate enzyme for nuclear RNA editing. Proc Natl Acad Sci USA 91:11457–11461, 1994

Kitamura K, Akamatsu S, Hirokawa K: Eine besondere Form der Akropigmentation: Acropigmentatio reticularis. Hautarzt 4:152–156, 1953

Li M, Jiang YX, Liu JB, *et al*: A novel mutation of DSRAD gene in a Chinese family with gyschromatosis symmetrica hereditaria. Clin Exp Dermatol 29: 533–535, 2004

Liu Q, Liu W, Jiang L, *et al*: Novel mutations of the RNA-specific adenosine deaminase gene (DSRAD) in Chinese families with dyschromatosis symmetrica hereditaria. J Invest Dermatol 122:896–899, 2004

Lomeli H, Mosbacher J, Melcher T, *et al*: Control of kinetic properties of AMPA channels by nuclear RNA editing. Science 266:1709–1713, 1994

Maas S, Rich A, Nishikura K: A-to-I RNA editing: Recent news and residual mysteries. J Biol Chem 278:1391–1394, 2003

Miyamura Y, Suzuki T, Kono M, Inagaki K, Ito S, Suzuki N, Tomita Y: Mutations of the RNA-specific adenosine deaminase gene (DSRAD) are involved in dyschromatosis symmetrica hereditaria. Am J Hum Genet 73:693–699, 2003

Nuber UA, Tinschert S, Mundlos S, Hauber I: Dyschromatosis universalis hereditaria: Familial case and ultrastructural skin investigation. Am J Med Genet 15:261–266, 2004

O'Connell MA, Krause S, Higuchi M, Hsuan JJ, Totty NF, Jenny A, Keller W: Cloning of cDNAs encoding mammalian double-stranded RNA-specific adenosine deaminase. Mol Cell Biol 15:1389–1397, 1995

Oyama M, Shimizu H, Ohata Y, Tajima S, Nishikawa T: Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): Report of a Japanese family with the condition and a literature review of 185 cases. Br J Dermatol 140:491–496, 1999

Polson AG, Bass BL, Casey JL: RNA editing of hepatitis delta virus antigenome by dsRNA-adenine deaminase. Nature 380:454–455, 1996

Rueter SM, Dawson TR, Emeson RB: Regulation of alternative splicing by RNA editing. Nature 399:75–80, 1999

Spritz RA, Holmes SA, Ramesar R, Greenberg J, Curtis D, Beighton P: Mutations of the KIT (mast/stem cell growth factor receptor) proto-oncogene account for a continuous range of phenotypes in human piebaldism. Am J Hum Genet 51:1058–1065, 1992

Toyama I: An unknown disorder of hyperpigmentation. Jpn J Dermatol Urol 10:644, 1910 (in Japanese).

Toyama I: Dyschromatosis symmetrica hereditaria. Jpn J Dermatol Urol 29: 95–96, 1929 (in Japanese)

Wagner RW, Smith JE, Cooperman BS, Nishikura K: A double-stranded RNA unwinding activity introduces structural alterations by means of adenosine to inosine conversions in mammalian cells and *Xenopus* eggs. Proc Natl Acad Sci USA 86:2647–2651, 1989

Wang Q, Miyakoda M, Yang W, Khillan J, Stachura DL, Weiss MJ, Nishikura K: Stress-induced apoptosis associated with null mutation of ADAR1 RNA editing deaminase gene. J Biol Chem 279:4952–4961, 2004

Xing Q, Wang M, Chen X, *et al*: A gene locus responsible for dyschromatosis symmetrica hereditaria (DSH) maps to chromosome 6q242–q252. Am J Hum Genet 73:377–382, 2003

Yang J-H, Luo X, Nie Y, *et al*: Widespread inosine-containing mRNA in lymphocytes regulated by ADAR1 in response to inflammation. Immunology 109:15–23, 2003

Zhang XJ, He PP, Li M, *et al*: Seven novel mutations of the ADAR gene in Chinese families and sporadic patients with dyschromatosis symmetrica hereditaria (DSH). Hum Mutat 23:629–630, 2004

Appendix

Electronic-database information Accession numbers and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for the cDNA of human *ADAR1* [accession number NM_ 001111], the genomic sequence of human *ADAR1* [accession number NT_004668])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM (for ADAR1, DSH and DUH)

dbSNP Home Page, http://www.ncbi.nlm.nih.gov/SNP/ (for ADAR1-1 [accession number rs17843863], ADAR1-2 [accession number rs17843864], ADAR1-3 [accession number rs17843870], ADAR1-4 [accession number rs17843865], ADAR1-5 [accession number rs17843866], ADAR1-6 [accession number rs17843867], ADAR1-7 [accession number rs17843868], ADAR1-8 [accession number rs17843869])