Dyschromatosis symmetrica hereditaria: A retrospective case series and literature review

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A B S T R A C T

Background/Objective: Dyschromatosis symmetrica hereditaria (DSH) is a rare pigmentary genodermatosis characterized by hyper- and hypopigmented macules on the face and dorsal aspects of the extremities. This study aimed to delineate the unique clinical, histological, and genetic features of DSH in a Taiwanese population.

Methods: A retrospective review of clinical charts and archival photographs was performed for patients diagnosed with DSH in a medical center in Taiwan between 1992 and 2011.

Results: A total of 25 patients (mean age at diagnosis 20.3 years) were given the clinical diagnosis of DSH. The male:female ratio was 14:11. Positive family history was noted in 16 patients (56%). The pattern of inheritance was basically autosomal dominant. Twelve patients (48%) had typical hypopigmented macules distributed on the dorsal aspects of the extremities. Six patients (24%) had coexistence of other diseases, particularly seizure, mental retardation, and autism. Mutation analyses were done on 12 patients (48%), with three novel mutations previously identified. Skin biopsy specimens were obtained from seven patients (28%). Six of those had pathological findings consistent with the diagnosis of DSH.

Conclusion: With this series, we hope to add to the DSH mutation database and contribute further to the understanding of DSH genotype/phenotype correlations.

Original Article

Introduction

Dyschromatosis symmetrica hereditaria (DSH, OMIM 127400), initially known as reticulated acropigmentation of Dohi, was first described by Toyama in 1929. It is a rare pigmentary genodermatosis that is characterized by onset of hyper- and hypopigmented macules on the face and dorsal aspects of the extremities in infancy or early childhood. DSH was previously reported mainly in Japanese and Chinese patients, but a few cases have been reported in different races including Koreans, Indians, Europeans, and South Americans. DSH generally shows an autosomal-dominant pattern of inheritance with high penetrance, but sporadic cases have been reported. Pathogenic mutations were identified in the double-stranded RNA-specific adenosine deaminase (ADAR1) gene. The ADAR1 gene, which spans 30 kb and contains 15 exons, is expressed ubiquitously all over the skin, but the molecular pathogenesis of DSH is yet to be clarified. Histological studies have shown abundant melanin pigment in the keratinocytes and melanocytes in the hyperpigmented macules and reduced melanization in hypopigmented macules.

Most articles so far were case reports especially of those with novel mutations of the ADAR1 gene. To our knowledge, we describe herein the largest series of patients with DSH in Taiwan—25 cases. Through these cases and literature review, we hope to delineate the unique clinical, histological, and genetic features of DSH.

Methods

We were able to identify 35 patients with clinical or pathological diagnosis of ‘dyschromatosis’ or ‘acropigmentation of Dohi’ in the computerized database at the Department of Dermatology at National Cheng-Kung University Hospital from 1992 to 2011. Six patients were excluded by pathological biopsy under the diagnoses of vitiligo, postinflammatory alternation, focal hypopigmentation, dyschromatotic amyloidosis, amyloidosis cutis dyschromica, and solar lentigo. Two other patients were excluded under the clinical diagnosis of dyschromatosis lentiginosa and dyschromatosis universalis hereditaria (DUH). Due to unavailable photographic documentation and being relatives of the index cases, two additional patients were also excluded. Based on characteristic clinical
features, 25 patients were identified under the clinical diagnosis of DSH. Clinical charts and archival photographs were reviewed to determine the distribution of skin lesions, age of onset, family history, and associated diseases. Experienced pathologists performed histological analyses for those who underwent skin biopsy. Mutational analysis of the ADAR1 gene was performed as previously described.7

Results

A total of 25 patients (mean age at diagnosis 20.3 years, range 3–68 years) were given the clinical diagnosis of DSH (Table 1). The male:female ratio was 14:11.

Fourteen index cases (56%) had disease onset between birth and childhood (up to an age of 8 years).8 A positive family history was noted in 14 patients (56%). Pattern of inheritance was basically autosomal dominant. Twelve patients (48%) had typical hypo- and hyperpigmented macules distributed on the dorsal aspects of the extremities (Figure 1). In addition to the extremities, two (8%) and one (4%) patients had cutaneous lesions distributed over trunk and neck, respectively, and 10 patients (40%) had freckle-like macules on the face. Six patients (24%) had coexistence of other diseases, including palmoplantar keratoderma, chronic urticaria, suspected collagen vascular disease, seizure, mental retardation, autism, keratoderma tylodes palmaris progressive, tardive dystonia, mood disorder, and psoriasis.

Mutation analyses

Twelve patients (48%) with genetic mutation analyses were further examined for family history, nucleotide change, amino-acid change, and position of mutation (Table 2).7,8,9,10 Three of the 12 patients (25%) did not demonstrate mutation in the ADAR1 gene but were still diagnosed with DSH based on clinical grounds. Four of the 12 patients (33%) did not have a family history of DSH, implicating a de novo origin. We have previously identified and published novel mutations found in Patients 2, 5, and 10.7,8,9,10

Histopathology

Skin biopsy specimens were obtained from seven patients (28%). Six of those had pathological findings consistent with the diagnosis of DSH. Fontana-Masson stain revealed hyper- and hypomelanization in hyper- and hypopigmented lesions, respectively. In Patient 5, immunostaining for Melan-A revealed normal density and morphology of basal melanocytes in the hypopigmented lesion but reduced number of basal melanocytes in the hypopigmented lesion.7 Ultrastructural study was done in Patient 10, which showed a large number of fully melanized melanosomes of varying sizes, often in large clusters, in the basal keratinocytes of hypopigmented macules.7 In the hypopigmented lesion, most keratinocytes showed few or no melanosomes. In both lesions, basal melanocytes were not easily found. In Patient 3, pathological findings showed vacuolar interface dermatis with focal epidermal atrophy and abundant melanophages, suggestive of collagen vascular disease. Immunostaining for Melan-A revealed scattered melanocytes along the basal layer in an uneven distribution and reduced in some foci. Nonetheless, the diagnosis of DSH was supported by mutation analysis.

Discussion

DSH was formerly considered to be a Japanese-specific genodermatosis, with a few cases reported among Koreans, Indians, Europeans, and South Americans. In the two reviews of the 185 reported cases from Japan3 and the 136 from China,4 clinical manifestations varied among different races or countries. In addition to the typical distribution of the extremities and face seen in Japanese, pigmentary change was noted on the neck and chest in the Chinese population. This may have implied that differences in the distribution of the skin lesions could be related to race and

Table 1 Clinicopathologic findings of patients with DSH.

<table>
<thead>
<tr>
<th>Patient no./sex/age at diagnosis (y)</th>
<th>Age (y) at onset</th>
<th>Pathology</th>
<th>Family history</th>
<th>Distribution</th>
<th>With other disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/28</td>
<td>10</td>
<td>DSH</td>
<td>?</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>2/M/7</td>
<td>3</td>
<td>?</td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>3/M/23</td>
<td>15</td>
<td>Suggestive of collagen vascular disease</td>
<td></td>
<td>E + trunk</td>
<td>PPK, chronic urticaria, poikiloderma, r/o collagen vascular disease or MF</td>
</tr>
<tr>
<td>4/M/20</td>
<td>Birth</td>
<td></td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>5/M/11</td>
<td>5</td>
<td>DSH</td>
<td></td>
<td>E + neck</td>
<td></td>
</tr>
<tr>
<td>6/F/10</td>
<td>?</td>
<td>+</td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>7/F/23</td>
<td>Childhood</td>
<td></td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>8/M/12</td>
<td>2</td>
<td>DSH</td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>9/F/18</td>
<td>2</td>
<td>?</td>
<td></td>
<td>F + E</td>
<td>Seizure disorder</td>
</tr>
<tr>
<td>10/M/7</td>
<td>1</td>
<td>DSH</td>
<td></td>
<td>F + E</td>
<td>Seizure, mental retardation, autism</td>
</tr>
<tr>
<td>11/F/48</td>
<td>Childhood</td>
<td></td>
<td></td>
<td>E</td>
<td>Chronic urticaria, KTPP</td>
</tr>
<tr>
<td>12/F/7</td>
<td>Childhood</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13/F/12</td>
<td>?</td>
<td></td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>14/F/31</td>
<td>?</td>
<td></td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>15/M/63</td>
<td>?</td>
<td></td>
<td></td>
<td>E + trunk</td>
<td></td>
</tr>
<tr>
<td>16/M/10</td>
<td>Birth</td>
<td>Uneven epidermal melanization</td>
<td>+</td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>17/F/18</td>
<td>13</td>
<td></td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>18/M/17</td>
<td>?</td>
<td>?</td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>19/M/5</td>
<td>2</td>
<td>+</td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>20/F/3</td>
<td>2</td>
<td>+</td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>21/M/3</td>
<td>?</td>
<td>?</td>
<td></td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>22/M/7</td>
<td>Birth</td>
<td></td>
<td></td>
<td>F + E</td>
<td></td>
</tr>
<tr>
<td>23/M/23</td>
<td>6</td>
<td></td>
<td></td>
<td>E</td>
<td>Tardive dystonia, mood disorder</td>
</tr>
<tr>
<td>24/F/20</td>
<td>?</td>
<td>+</td>
<td></td>
<td>E</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>25/M/68</td>
<td>?</td>
<td>+</td>
<td></td>
<td>E</td>
<td></td>
</tr>
</tbody>
</table>

DDD – Dowling–Degos disease; DUH – dyschromatosis universalis hereditaria; E – extremities; F – face; KTPP – keratoderma tylodes palmaris progressive; MF – mycosis fungoides; PPK – palmoplantar keratoderma; – – finding absent; + – finding present.
Adenosine deaminase acting on the RNA (ADARs) represents one type of RNA-editing enzyme. It catalyzes deamination of adenosine to inosine in dsRNA. This alteration has been demonstrated to promote the survival and function of many tissues, including vertebra, heart, liver, and brain. Specifically, ADAR1 is essential for maintenance of hematopoiesis in the fetal liver and adult bone marrow. It is also an essential suppressor of interferon signaling that may protect organisms from the deleterious effects of interferon activation associated with many pathological processes including chronic inflammation, autoimmune disorders, and cancer. Genetic mutation in the double-stranded RNA-specific adenosine deaminase (ADAR1) gene is responsible for the altered production or distribution of melanin to the units of epidermal melanization. ADAR1 protein's target gene(s) in the skin still remains unknown. Two isoforms of ADAR1 protein are generated by translation from distinct transcripts directed by different promoters: an interferon-inducible full-length ADAR1 (p150) and a constitutively expressed N-terminal truncated ADAR1 protein (p110). Kondo et al suggested that only the p150 protein and the interferon-inducible mechanism may be responsible for the etiology of DSH. It has been reported that the p150 protein is involved in antiapoptotic pathways and also appears to regulate cellular siRNA. Taken these together, perhaps the melanocytes harboring ADAR1 mutation are more prone to proapoptotic stimuli that resulted in melanocyte depletion seen in hypopigmented lesions. It is unknown why pigmentary changes in DSH are localized specifically on dorsum of hands and feet. Miyamura et al speculated that during development, distal migration of melanoblasts from the neural crest to the skin is associated with a greater reduction in ADAR activity at anatomic sites most distant from the neural crest. Impaired RNA editing from adenosine to inosine may result in differentiations of melanoblasts into either hyper- or hypoactive melanocytes that colonize the skin in an irregular distribution. This may contribute to the preferential distribution of the mottled hyper- and hypopigmentation seen on dorsum of hands and feet in DSH. Although DSH generally shows an autosomal-dominant pattern of inheritance with high penetrance, clinical features were not always similar among the patients in

Table 2 Molecular findings of patients with mutation analysis of the ADAR1 gene.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Family history</th>
<th>Age (y) at onset</th>
<th>Nucleotide change</th>
<th>Amino-acid change</th>
<th>Position</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unknown</td>
<td>10</td>
<td>Negative</td>
<td>Q693X</td>
<td>Exon 5</td>
<td>Nonsense*</td>
</tr>
<tr>
<td>2</td>
<td>Familial</td>
<td>3</td>
<td>2077C&gt;T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Familial</td>
<td>15</td>
<td>1760A&gt;G</td>
<td>Y587C</td>
<td>Exon 3</td>
<td>Missense</td>
</tr>
<tr>
<td>4</td>
<td>Familial</td>
<td>Birth</td>
<td>c.2433_2434delAG</td>
<td>p.T811fs</td>
<td>Exon 7</td>
<td>Deletion</td>
</tr>
<tr>
<td>5</td>
<td>Sporadic</td>
<td>5</td>
<td>2433delA</td>
<td>p.T811fs</td>
<td>Exon 14</td>
<td>Missense</td>
</tr>
<tr>
<td>6</td>
<td>Familial</td>
<td>Unknown</td>
<td>3359A&gt;G</td>
<td>K1120R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Unknown</td>
<td>Childhood</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sporadic</td>
<td>2</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
<td>2</td>
<td>CAG&gt;GAG</td>
<td>Q693E</td>
<td>Exon 5</td>
<td>Missense</td>
</tr>
<tr>
<td>10</td>
<td>Sporadic</td>
<td>1</td>
<td>2645delG</td>
<td>PTC+13aa</td>
<td>Exon 8</td>
<td>Deletion</td>
</tr>
<tr>
<td>11</td>
<td>Familial</td>
<td>Childhood</td>
<td>2077C&gt;T</td>
<td>Q691X</td>
<td>Exon 5</td>
<td>Nonsense</td>
</tr>
<tr>
<td>12</td>
<td>Familial</td>
<td>Childhood</td>
<td>IVS6 +2 T&gt;G</td>
<td></td>
<td>Intron 6</td>
<td></td>
</tr>
</tbody>
</table>

* Novel mutations previously identified.7,8,9,10
melanocyte counts in both hyper- and hypopigmented lesions.\textsuperscript{19,20}

been noted, mainly in the West.\textsuperscript{17} We have previously identi
but cases of autosomal-recessive type and spontaneous origin have

could not claim conclusive hot spot for mutations in our study. DSH
limited number of patients with mutation analysis in this series, we

Patients 2, 9, and 11 had mutation located in DRBM2, whereas

binding domains and three dsRNA-binding motif (DRBM) repeats.

vigorous protection from sunlight is still encouraged.

alterations in DSH. Due to the current lack of active treatment,

phenotypic variations and no evident genotype
e

ans, some variable environmental factors such as sun exposure could influence
the phenotype expression to some extent.\textsuperscript{13} We have previously
discussed the possible role of sunlight in the pathogenesis of DSH.\textsuperscript{10}
The index case developed asymptomatic mixture of small hyper-

and hypopigmented macules on the back of the hands and feet in

childhood. DSH was further confirmed with mutation analysis, in
which the daughter and younger sister of the index case had the
same mutation. Significant improvement of the dyspigmentation
was seen after strict sun protection. This may suggest that some
variable environmental factors such as sun exposure could influence
the phenotypes.\textsuperscript{10} Further studies are needed to elucidate the
role of sunlight in the pathogenesis and/or progression of pigment
alterations in DSH. Due to the current lack of active treatment,
vigorous protection from sunlight is still encouraged.

According to Lai et al,\textsuperscript{15} more than 122 different ADAR1 muta-
tions have been detected. The full-length 12266-aa ADAR1 protein
contains six functional domains including dsRNA adenosine
deaminase do
domain (ADEAmc). The ADEAmc, which encompasses
amo

acidos 886–1221, has been proposed as a hot spot for muta-
tions.\textsuperscript{16} About 62% of the currently known mutations for DSH have
been reported in this domain.\textsuperscript{15} Patient 6 had a missense mutation
located within this domain. The other domains are two Z-DNA-

binding domains and three dsRNA-binding motif (DRBM) repeats.

Patients 2, 9, and 11 had mutation located in DRBM2, whereas

Patients 3 and 4 in DRBM1 and DRBM3, respectively. Due to the
limited number of patients with mutation analysis in this series, we
could not claim conclusive hot spot for mutations in our study. DSH
generally shows an autosomal-dominant pattern of inheritance,
but cases of autosomal-recessive type and spontaneous origin have
been noted, mainly in the West.\textsuperscript{17} We have previously identified
two novel deletion mutations of the ADAR1 gene.\textsuperscript{7,18} Family pedigree
of both patients suggested sporadic cases of DSH. To date, clinical
manifestations observed in patients with DSH showed no obvious
phenotypic variations and no evident genotype–phenotype correla-
tions between affected individuals.\textsuperscript{18} No correlation was
found between the extent of skin lesions and the mutations sites.\textsuperscript{13}

Even in the same pedigree, the extent of skin lesions differed
among patients. As mentioned earlier, some variable environ-
mental factors such as sun exposure could influence the
phenotypes.\textsuperscript{10}

Histological studies characteristically show abundant melanin
pigment in keratinocytes and melanocytes in hyperpigmented
macules but reduced melanization in hypopigmented ones.\textsuperscript{3} To
assess epidermal melanization and melanocytic density, Masson-

Fontana staining and immunostaining for S-100 and Melan-A are
helpful. From experience, we believe that Melan-A is superior to S-

100 in displaying better morphology and larger number of mela-

nocytes in the epidermis.\textsuperscript{7} Sheu and Yu noted decreased epidermal
melanocyte counts in both hyper- and hypopigmented lesions.\textsuperscript{19,20}

Similarly in our data, Patients 8 and 10 showed reduced number of
melanocytes in both lesions. Patient 5, however, had normal and
reduced number of melanocytes in the hyper- and hypopigmented
macules, respectively. The difference might be attributable to the
different sampling or assessment methods. Ultrastructural study
was done in Patient 10, which revealed large clusters of melano-
somes in the keratinocytes and a few melanocytes with dendrites
containing melanosomes.\textsuperscript{9} In the hypopigmented lesion, melano-
cytes were small and not easily found. Most keratinocytes showed
few or no melanosomes. Our findings are consistent with those of
previous reports. Sheu and Yu precisely described small or immu-
nate melanosomes scattered sparsely in the melanocytes but many
small ones in the adjacent keratinocytes in the hyperpigmented
area.\textsuperscript{20} Melanocyte abnormalities of the hypomelanic skin
included decrease in the number of melanocytes, fatty degenera-
tion, swollen mitochondria, large vacuolization of the cytoplasm,
and condensed, irregularly shaped nucleus.\textsuperscript{20}

In general, DSH is not accompanied by systemic involvement or
common associated disorder.\textsuperscript{3} Despite the rarity of extracutaneous
manifestations, we have previously identified Patient 10 with DSH
and seizure, mental retardation, and autistic disorder.\textsuperscript{5} Similarly,
Patients 9 and 23 also had the coexistence of seizure and tardive
dystonia with mood disorder, respectively. Hypotonia, mental
retardation, agitation, schizophrenia, type 1 neurofibromatosis,
thalassemia, polydactyly, and torsion dystonia had been observed
in other cases of DSH elsewhere.\textsuperscript{17,21} Tojo et al\textsuperscript{22} reported a muta-
tion of p.G1007R in the ADAR1 gene in a DSH patient accompanied
by dystonia and mental deterioration. Interestingly, the same
mutation was also reported by Kondo et al\textsuperscript{23} in a DSH patient
associated with dystonia, mental deterioration, and brain calcifica-
tion. Clearly, the relationship between DSH and neurological or
mental disorder deserves to be further clarified. In Patient 25, we
also observed association with psoriasis. Shi et al recently reported
the coexistence of DSH and psoriasis in a 28-year-old man. He had
a single-nucleotide transversion (T to A at the base 2632) and
a two-nucleotide deletion (2633–2634delCT) in the ADAR1 gene.\textsuperscript{24}
The patient had no family history of psoriasis. Because both
diseases are quite different in entities, coexistence of these two
unrelated diseases may simply be coincidental without signi-

ficant intrinsic factors.

A differential diagnosis of DSH should include reticulate
acropigmentation of Kitamura, DUH, Dowling–Degos disease
(DDD), a mild form of xeroderma pigmentosum, and pigment
 disorders due to exposure to chemicals or radiation.\textsuperscript{1,2} A 45-year-old
female patient was presented to our clinic with asymptomatic
mottled pigmentation over neck for 15 years and a positive family
history. Under the clinical impression of DSH, skin biopsy and
mutation analysis were performed, which showed solar lentigo
and negative finding, respectively. As a result, DDD was more likely.
Clinically, DDD also displayed mottled hyper- and hypopigmented

| Table 3 Comparison of patients with dyschromatosis symmetrica hereditaria in other studies. |
|---------------------------------|----------------|----------------|
| **NCKUH in Taiwan**              | **Japan**      | **China**      |
| No. of cases                    | 25             | 185            |
| Onset                          | Birth to childhood\textsuperscript{a} 14/25 (56%) | ≤5 y. 91/185 (73%) |
| Gender: M/F                    | 14:11 – 1.27   | 93:85 – 1.09   |
| Positive family Hx             | 14/25 (56%)    | 114/185 (61%)  |
| Inheritance pattern            | AD, 14/25 (56%) | AD            |
| Distribution                    | F + E: 10/25 (40%) | F + E: 65/152 (43%) |
|                                | E: 12/25 (48%) | E: 75/152 (49%) |
|                                | E + trunk: 2/25 (8%) | E + neck + chest: 1/17 (18%) |
|                                | E + neck: 1/25 (4%) | E + F + neck + chest: 2/17 (12%) |

AD = autosomal dominant; E = extremities; F = face; Hx = history; NCKUH = National Cheng Kung University Hospital.

\textsuperscript{a} According to the National Association for the Education of Young Children, early childhood spans from birth to 8 years of age.
DUH was initially described by Ichikawa and Hiraga in 1933. Based on the clinical and histological findings, DUH lesions showed epidermal hypermelanization without melanocytic involvement. The hematoxylin and eosin-stained specimens taken from the hypopigmented lesions revealed melanocytopenia with marked hypomelanization. Findings from the hypopigmented lesion showed epidermal hypermelanization without melanocytopenia. Based on the clinical and histological findings with negative mutation analysis, a diagnosis of DUH was made for this patient (Figure 2). DUH was initially described by Ichikawa and Hiraga in 1933. Typical DUH skin lesions were characterized by numerous hyper- and hypopigmented macules of various sizes seen on the trunk and limbs, including the dorsal of the hands and feet. Facial lesions are seen in 50% of affected individuals. DUH usually has autosomal-dominant inheritance, but a few cases of autosomal-recessive inheritance and spontaneous origin have been described. Two loci responsible for the disease have been identified: one on chromosome 6q24.2–q25.2 in two Chinese families and another on chromosome 12q21–q23 in an Arab population. In spite of the similarity in phenotypes, DSH and DUH are genetically distinct disorders.

Currently, there is no set of diagnostic criteria for DSH. Clinically, DSH is characterized by hyper- and hypopigmented macules on the dorsum of hands and feet appearing in infancy or early childhood. Pathological findings allow us to assess epidermal melanization but may not show consistent findings due to different sampling or assessment methods. In 2003, the Chinese and Japanese groups have identified pathogenic mutations in the ADAR1 gene. Prior to this, most of our cases were diagnosed with DSH based on clinical-pathologic grounds. After 2003, however, the diagnosis is largely supported by mutation analysis, especially in doubtful cases.

Limitations of this study include retrospective design, referral bias, limited number of cases, and lack of mutation and histological analyses performed on all patients. In summary, with a series of 25 patients with DSH, we hope to provide addition to the DSH mutation database and contribute further to the understanding of DSH genotype/phenotype correlations. The variety of clinical phenotypes even in the pedigree may suggest presence of factors other than the ADAR1 gene. The relationship between DSH and neurological or mental disorder also deserves to be further elucidated.

References


