

Novel De Novo Heterozygous Frameshift Mutation of the *ADAR1* Gene in Heavy Dyschromatosis Symmetrica Hereditaria

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PRACTICE POINTS

- The adenosine deaminase RNA specific gene, *ADAR1*, has been identified as being responsible for the development of dyschromatosis symmetrica hereditaria (DSH).
- The characteristic appearance of DSH is a mixture of hyperpigmented and hypopigmented macules of various sizes on the dorsal aspects of the hands and feet.

To the Editor:

Dyschromatosis symmetrica hereditaria (DSH) (Online Mendelian Inheritance in Man 127400), also called reticulate acropigmentation of Dohi, is a pigmentary genodermatosis characterized by a mixture of hyperpigmented and hypopigmented macules of various sizes on the dorsal aspects of the hands and feet. Linkage analysis has revealed that the DSH gene locus resides on chromosome 1q11-q21,¹ and the adenosine deaminase RNA specific gene, *ADAR1* (also called *DSRAD*), in this region has been identified as being responsible for the development of DSH.² We report a sporadic case of severe DSH with the *ADAR1* gene detected in a mutation analysis.

A 6-year-old girl presented with a mixture of hyperpigmented and hypopigmented macules on the dorsal aspects of the hands and feet and the curved side of the wrists, heels, and knees, as well as scattered frecklelike and depigmented spots on the face, ears, neck, arms, and upper back (Figure 1). Her parents noted that hyperpigmented and hypopigmented macules on the dorsal aspects of the hands developed at 5 months of age. Exacerbation after exposure to sunlight resulted in the eruption becoming remarkable in summer and fainter in winter. The skin lesions gradually became more progressive. Physical examination revealed that the patient generally was healthy.

After obtaining informed consent, we performed a mutation analysis of the *ADAR1* gene in our patient and her parents. We used a kit to extract genomic DNA from peripheral blood, which was then used to amplify the exons of the *ADAR1* gene with intronic flanking sequences by polymerase chain reaction with the primer.³ After amplification, polymerase chain reaction products were purified. We sequenced the *ADAR1* gene. Sequence comparisons and analysis found that the patient (proband) carried a heterozygous insertional mutation c.2253insG in exon 6 of the *ADAR1* gene. This mutation was not detected in the proband's healthy parents and 100 normal individuals (Figure 2).

Dyschromatosis symmetrica hereditaria is acquired by autosomal-dominant inheritance and is

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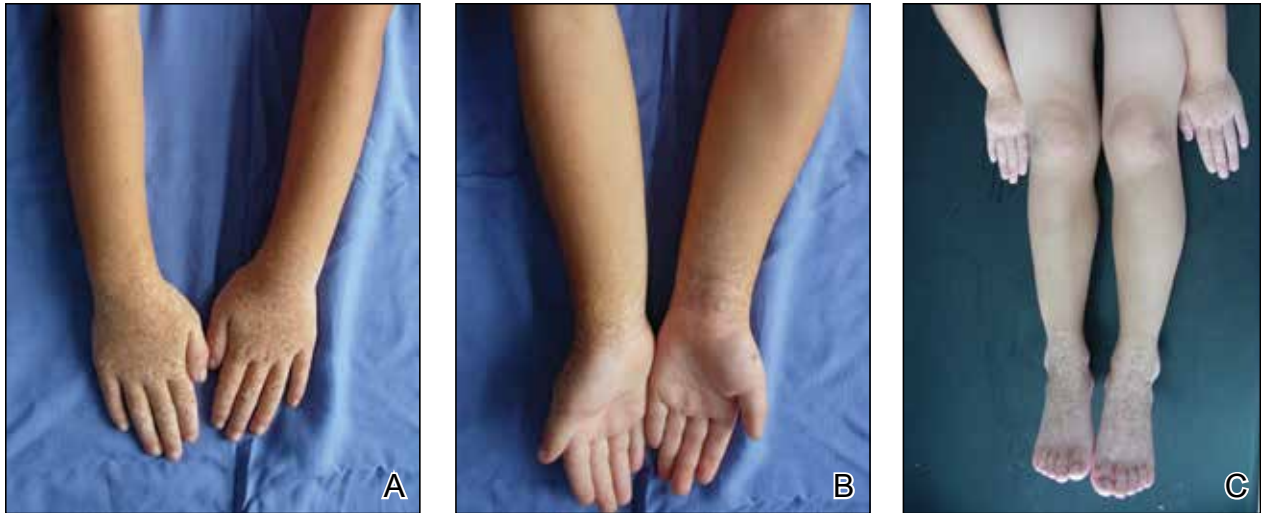


Figure 1. A mixture of hyperpigmented and hypopigmented macules on the dorsal aspects of the hands (A), curved side of the wrists (B), knees, and dorsal aspects of the feet (C).

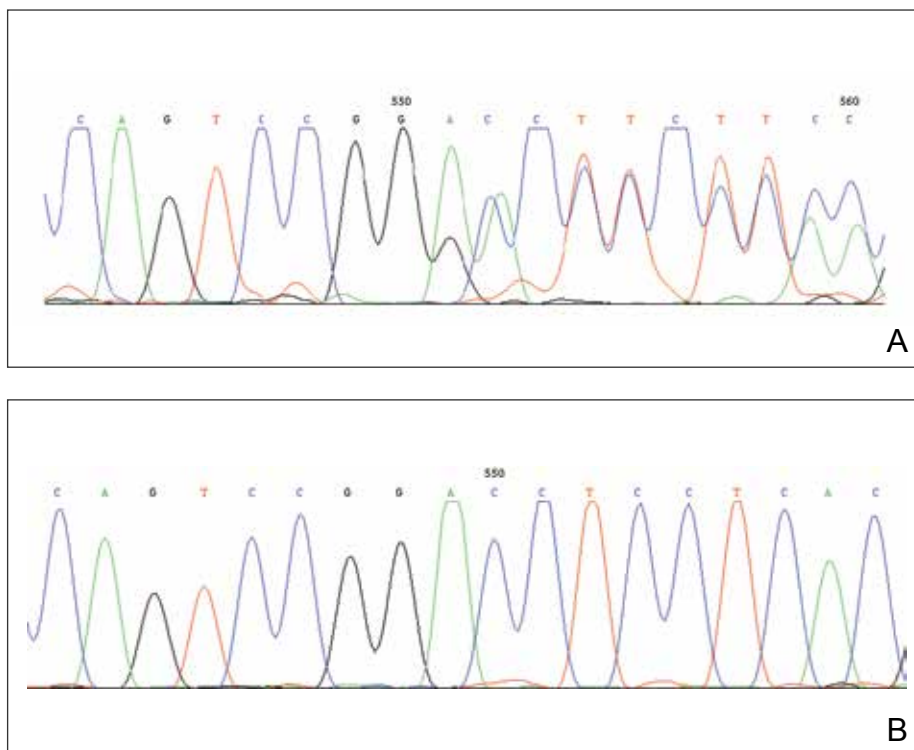


Figure 2. Identification of the *ADAR1* (adenosine deaminase RNA specific) gene mutation with a heterozygous insertion mutation c.2253insG in exon 6 (A) and wild-type allele in a normal control in exon 6 (B).

mainly reported in Asians, especially in Japan and China. Oyama et al⁴ reviewed 185 cases of DSH in Japan and found the onset of this disease usually was during infancy or childhood; 73% of patients developed the skin lesions before 6 years of age. Suzuki et al⁵ reported 10 unrelated Japanese patients and found the onset of disease ranged from 1 year of age to childhood. Zhang et al^{1,6} investigated 78 Chinese

patients with DSH including 8 multigenerational families and 2 sporadic patients and found the age of disease onset ranged from 6 months to 15 years of age. The age of onset in our patient (5 months) was younger than these prior reports.

Patients with DSH have a characteristic appearance including a mixture of hyperpigmented and hypopigmented macules of various sizes on the dorsal

aspects of the hands and feet. Few patients have similar lesions on the knees and elbows. Many patients have frecklelike macules on the face and arms.¹⁻⁶ One patient has been described with scattered depigmented spots on the face and chest.¹ Our patient had a characteristic appearance as well as some special manifestations including skin lesions on the curved side of the wrist, ears, neck, and upper back.

The human *ADAR1* gene spans 30 kilobase and contains 15 exons. It encodes RNA-specific adenosine deaminase composed of 1226 amino acid residues. This enzyme is important for various functions such as site-specific RNA editing and nuclear translation. This enzyme has 2 Z-alpha domains, 3 double-stranded RNA-binding domains, and the putative deaminase domain corresponding to exon 2, exons 2 to 7, and exons 9 to 14 of *ADAR1*, respectively.⁶

Mutation analysis of the *ADAR1* gene in this case showed heterozygous insertion mutation c.2253insG in exon 6 of the *ADAR1* gene, which changed the reading frame, and 475 amino acid residues in C-terminus are replaced by 90 amino acid residues (TSSRAQVRLPSKSWGSLVPSRLRTQQEA RQAGSSRCGSPCLDWGEREGRTHGFHRG NPSDRGQSQKNYA PPLK VPRSTAKT DTPSHWQHLP). This mutation was not detected in the proband's healthy parents and the 100 control individuals, which indicated that it was a de novo mutation and the pathogenic mutation of DSH rather than a common polymorphism.

In conclusion, we report a novel mutation of the *ADAR1* gene with a heavy clinical phenotype in

DSH. This study expands the spectrum of clinical manifestations and demonstrates the *ADAR1* mutation in DSH.

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