CORRESPONDENCE

A novel deletion mutation in the adenosine deaminase RNA-specific gene in a Taiwanese patient with dyschromatosis symmetrica hereditaria

Case report

A 10-year-old boy was referred to our dermatology department with mottled hyperpigmented and hypopigmented macules over the upper extremities and neck for about 5 years (Figure 1). There was no history of prolonged sun exposure. The skin lesions were more prominent in summer and improved in winter. He was otherwise healthy except for allergic rhinitis. No other family members had similar skin lesions.

Skin biopsies were done from a hyperpigmented macule and a hypopigmented macule. The hyperpigmented lesion showed basal hyperpigmentation; the density and morphology of basal melanocytes appeared normal as demonstrated by immunostaining for Melan-A. The hypopigmented lesion showed basal hypopigmentation with reduced number of Melan-A-positive basal melanocytes. The clinical and pathologic findings are consistent with dyschromatosis symmetrica hereditaria (DSH).

Polymerase chain reaction amplification and automated sequencing

Genomic DNA was extracted from peripheral blood of the patient with informed consent from patient’s parents. DNA sample was then subjected to mutation screening by amplification of segments of adenosine deaminase RNA-specific (ADAR) gene. For polymerase chain reaction (PCR) amplification, approximately 200 ng of genomic DNA, 12.8 pmol/L of each primer, 10 μmole/L dNTP, and 1.25 U of AmpliTaq Gold (Perkin Elmer, Roche Molecular Systems, Inc., Branchburg, NJ, USA) were used in a total volume of 50 μL. The oligonucleotide primers designed to amplify the mutation in Exon 7 of the ADAR gene were: forward primer, 5'-GTAATACCTGGATGTGGCAC-3' and reverse primer, 5'-GTCCCAGTTACTGCTCTCTC-3'. The product size was 556 base pairs. The amplification conditions were 94°C for 5 minutes followed by 35 cycles of 94°C for 45 seconds, annealing temperature (50°C for 45 seconds and 72°C for 45 seconds), and final extension at 72°C for 10 minutes. The PCR products were examined on 2% agarose gel. The PCR product was subjected to direct automated sequencing (377 ABI Advanced Biotechnologies, Columbia, MD, USA).

A deletion mutation, c.2433delA (p.T811fs), resulting in premature termination code (PTC + 33 aa) was found (Figure 2).

Discussion

We described the clinicopathologic findings of DSH in a Taiwanese boy. The diagnosis of DSH was supported by mutation analysis, which detected a novel deletion mutation in the ADAR gene. The family pedigree suggested that our patient is a sporadic case of DSH. DSH (OMIM 127400), also known as 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 extremities and freckle-like macules on the face. It was first described by Toyama in a Japanese family in 1929 and was later reported mainly in Japanese and Chinese patients, with a few cases reported among Koreans, Indians, Europeans, and South Americans. DSH shows autosomal dominant pattern of inheritance, but sporadic cases have been reported. ADAR gene is also known as adenosine deaminase acting on RNA 1 gene or double-stranded RNA-specific adenosine deaminase gene, which encodes ADAR. The gene contains six functional domains, including two Z-DNA-binding domain in adenosine deaminases (Z-alpha), three double-stranded RNA binding motifs (DSRM),

Figure 1 Our patient, a 10-year-old boy, presented with mottled hyperpigmented and hypopigmented macules on the (A) neck, (B) right upper arm, and (C) left lower arm.
and one tRNA-specific and dsRNA adenosine deaminase domain (ADAMc). The ADAMc encodes the amino acid residues from 886 to 1221, which is only about 27% of the total 1226 amino acid residues in length. However, 63 different mutations have been reported in this domain, accounting for nearly 70% of the known 93 mutations for DSH.

ADAR catalyzes the deamination of adenosine to inosine in dsRNA, which produces changes in the codon or splice site and destabilizes the dsRNA helix. Two different concepts, namely haploinsufficiency and a dominant-negative effect because of the absence of homodimerization, have been proposed as the possible molecular pathogenesis of DSH. The adenosine to inosine alteration has been demonstrated to promote the survival and function of many tissues, including vertebra, heart, liver, and brain. ADAR is also expressed ubiquitously all over the skin. Miyamura et al speculated that distal migration of melanoblasts from the neural crest to the skin during development is associated with a greater reduction in ADAR activity at anatomic sites most distant from the neural crest. Failure of adenosine to inosine RNA editing may cause melanoblasts to differentiate into either hyperactive or hypoactive melanocytes, which then colonize the skin in an irregular distribution. This may explain the mottled hyperpigmented and hypopigmented macular dyschromatosis of DSH and their preferential distribution on the backs of the hands and feet.

DSH usually begins during infancy or early childhood. The clinical manifestation varies among different races or countries. In the two reviews of the 185 reported cases from Japan and the 136 reported cases from China, the latter showed extraordinary pigmentation change on the neck and the chest in addition to the typical distribution of the extremities and face observed in the former. The skin manifestation in the present patient as well as our other patients are similar to those reported from China. Nevertheless, no obvious correlation between genotype and phenotype has been discovered yet. Besides, positive family history was noted in 77.6% of the Japanese patients. The data are similar to the result as the more homogenous appearance of the skin color might be because of the reduced pigmentation of the hyperpigmented components. However, the role of sunlight in the pathogenesis and/or progression of pigment alterations as well as the potential beneficial effect of strict sun protection need to be further elucidated.

Acknowledgments

This study was supported by grant NSC95–2314–B006–042 from the National Science Council, Taiwan.

References