QUIZ SECTION

Hyper- and Hypo-pigmented Small Macules on Face, Neck and Extremities: A Quiz

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A 6-year-old girl presented at our dermatology clinic with asymptomatic macules on her face, neck and dorsal aspects of the hands, knees, and feet (Fig. 1). The lesions had started at approximately 8 months of age and initially involved the hands. The lesions gradually became prominent, especially after sun exposure. Her mother recalled having similar lesions on her hands and feet since early childhood. Physical examination showed a mixture of irregularly shaped hyper- or hypo-pigmented macules of varying sizes on the dorsal aspects of the patient's neck, hands and feet. There were freckle-like macules on her cheeks.

What is your diagnosis? See next page for answer.

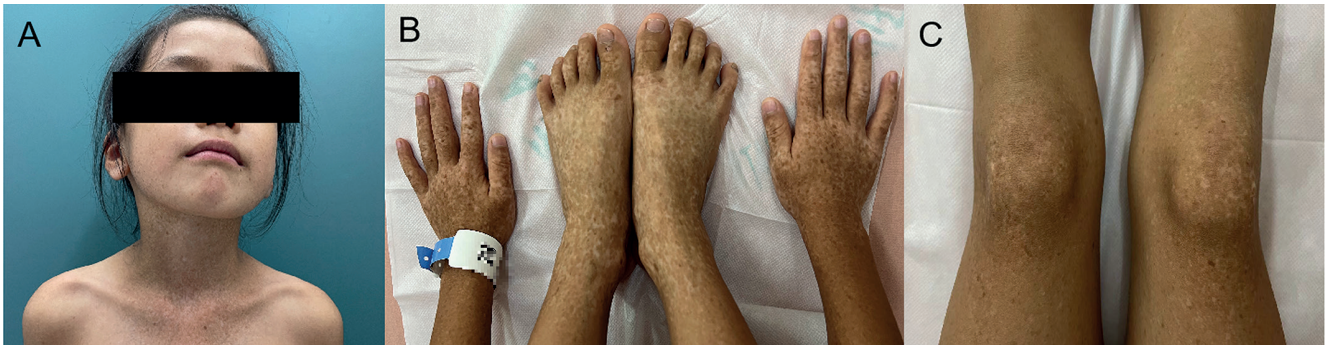

Fig. 1. Skin features of the patient. Hyperpigmented and hypopigmented macules on (A) face and neck, (B) extremities and (C) knee joints.

ANSWERS TO QUIZ

Hyper- and Hypo-pigmented Small Macules on Face, Neck and Extremities: A Commentary

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Diagnosis: **Dyschromatosis symmetrica hereditaria (DSH)**

Whole exome sequencing was performed. The study was approved by the local institutional review board, and the patient's parents provided written informed consent. A novel heterozygous frame-shift mutation (c.2337_2338dup:p.Gly780Glufs*14) was identified in the exon 1 of the *ADAR1* gene, which generated a pre-termination 13 codons downstream of the duplication site (Fig. 2).

DSH is an autosomal dominant pigmentary disorder, mainly reported in Japan and China, although genetically confirmed cases have been reported in other countries. It is clinically characterized by the presence of hyperpigmented and hypopigmented macules, mostly on the dorsal of the extremities, which first appear in infancy or early adolescence and last for life. Histopathologically, the numbers of melanocytes in hypopigmented macules are lower than in normal skin (1). The vast majority of DSH only manifest skin symptoms, whilst a few patients have been reported to develop neurological complications, such as dystonia and mental deterioration (2). Differential diagnoses of DSH include reticulate acropigmentation of Kitamura (RA), dyschromatosis universalis hereditaria (DUH) and mild or early-stage xeroderma pigmentosum (XP) (3). RA is characterized by atrophic pigmented macules on the dorsal aspect of the hands, feet, and palmoplantar pits. DUH presents with hyper- and hypopigmented macules distributed all over the body. XP is distinguished from DSH by the development of progressively worsening skin symptoms, such as xerosis, atrophy, telangiectasia, and skin tumours on sun-exposed areas and a high risk of neurological involvement.

The gene responsible for DSH has been identified as adenosine deaminase acting on RNA1 (*ADAR1*). The ADAR1 protein is essential for RNA editing, mostly adenosine (A)-to- inosine (I) RNA editing of post-transcriptional modifications, modifying to A to I in pre-mRNA and is involved in various activities, such as viral inactivation, structural change of the protein and the resultant cell survival (4). However, its function in the skin and role in the pathogenesis of DSH are unknown. To date, more than 200 mutations in the *ADAR1* gene have been reported to be associated with the disorder, including nonsense, missense, frameshift and splice-site mutations (5). These mutations could induce a premature translation termination codon and further translate into a truncated protein, which might be degraded by nonsense-mediated mRNA decay and result in haploinsufficiency, or not be degraded but become harmful to affect the normal function. Some treatments, including sunscreen for DSH, have been proposed, but no causal therapies have been developed to date (6).

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The patient provided written informed consent to the publication of their case details.

The authors have no conflicts of interest to declare.

REFERENCES

1. Kono M, Akiyama M. Dyschromatosis symmetrica hereditaria and reticulate acropigmentation of Kitamura: an update. J Dermatol Sci 2019; 93: 75–81.
2. Kondo T, Suzuki T, Ito S, Kono M, Negoro T, Tomita Y. Dyschromatosis symmetrica hereditaria associated with neurological disorders. J Dermatol 2008; 35: 662–666.
3. Hayashi M, Suzuki T. Dyschromatosis symmetrica hereditaria. J Dermatol 2013; 40: 336–343.
4. Song B, Shiromoto Y, Minakuchi M, Nishikura K. The role of RNA editing enzyme ADAR1 in human disease. Wiley Interdiscip Rev RNA 2022; 13: e1665.
5. Wang P, Yu S, Liu J, Zhang D, Kang X. Seven novel mutations of ADAR in multi-ethnic pedigrees with dyschromatosis symmetrica hereditaria in China. Mol Genet Genomic Med 2019; 7: e00905.
6. Kono M, Okamoto T, Takeichi T, Muro Y, Akiyama M. Dyschromatosis symmetrica hereditaria may be successfully controlled by topical sunscreen. Eur J Dermatol 2018; 28: 840–841.

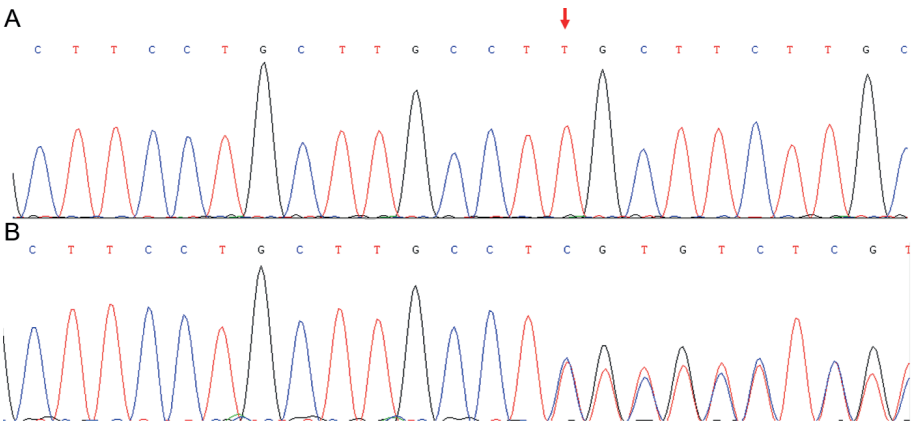

Fig. 2. Sequence analysis and mutations analysis. (A) Sequence of exon 1 of the *ADAR1* gene in normal subjects. (B) c.2337_2338dup (p.Gly780Glufs) heterozygous mutation in exon 1 of the *ADAR1* gene, based on peripheral blood leukocyte DNA from the patient.