Net Letter

A novel missense mutation in ADAR1 gene causing dyschromatosis symmetrica hereditaria in a Chinese patient

Dyschromatosis symmetrica hereditaria, also called reticulate acropigmentation of Dohi, is an autosomal dominant, cutaneous disease characterized by asymptomatic, hyperpigmented and hypopigmented macules on the dorsal aspects of the extremities. Heterozygous mutations in the adenosine deaminase acting on RNA 1 (*ADAR1*) gene were identified as the molecular basis of dyschromatosis symmetrica hereditaria.[1]

In this study, we investigated the members of a four-generation family from Jiangsu province of China with typical dyschromatosis symmetrica hereditaria [Figure 1a]. The proband of this family is a 60-year-old male with a history, from 6 to 7 months age, of hyperpigmented and hypopigmented macules on the distal extremities [Figure 1b and c]. The typical lesions were also observed on the knees, elbows [Figure 1d], and buttocks [Figure 1e]. After informed consent, we collected peripheral blood from the patient and sequenced all exons of the *ADAR1* gene. We detected a heterozygous missense mutation (c. 3026G > A) in the *ADAR1* gene in the patient [Figure 1f]. The *ADAR1* gene mutation was, however, not detected in 100 unrelated controls [Figure 1g].

A previous study demonstrated that a heterozygous mutation of *ADAR1* causes dyschromatosis symmetrica hereditaria,[1] and so far, more than 120 mutations in the *ADAR1* gene have been reported.[2] The deaminase domain, located between positions 886 to 1221 of the *ADAR1* gene, covers more than 50% of the reported mutations.[2] This domain is critical for enzyme function and is thought to play an important role in the pathogenesis of dyschromatosis symmetrica hereditaria. The missense mutation c. 3026G > A, which was identified in the patient, is located in the deaminase domain of the *ADAR1* protein in exon 12. Mutations in exon 12 have also been reported in other unrelated families,[2] and this result further supported the speculation that the deaminase domain might be a hot spot for mutations. The new missense mutation

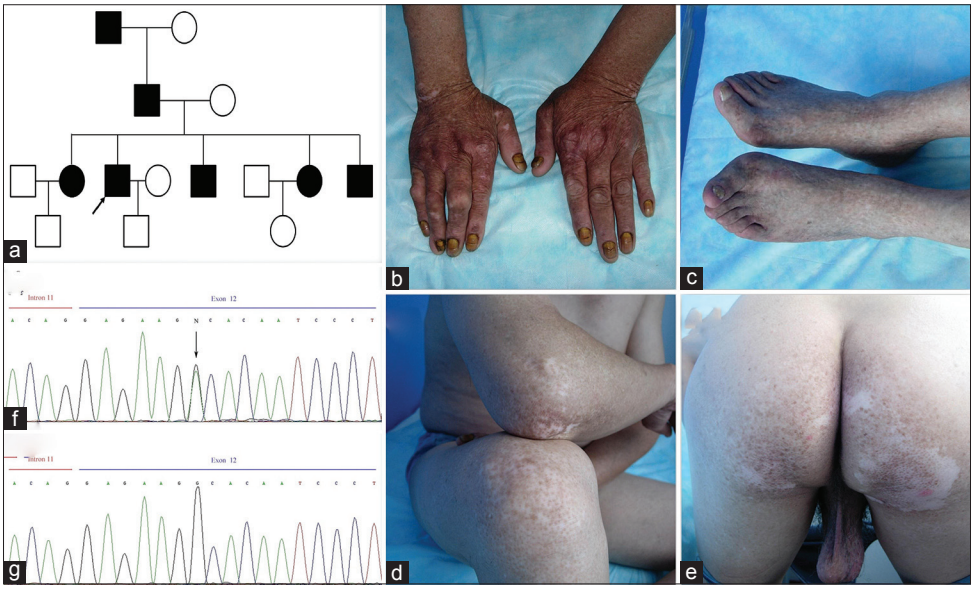

Figure 1: Identifying lesions and characterizing a novel mutation in the *ADAR1* gene in a proband of a family affected with dyschromatosis symmetrica hereditaria. (a) Pedigree of the family. Affected family members are represented by black symbols. The proband is indicated by an arrow. (b) Hypopigmented and hyperpigmented macules on the back of the hand. (c) Hypopigmented and hyperpigmented macules on the lower limbs. (d) Hypopigmented and hyperpigmented macules on the elbows. (e) Hypopigmented and hyperpigmented macules on the buttocks. (f) Novel c. 3026G > A mutation of the *ADAR1* gene observed in the patient. (g) Normal *ADAR1* gene sequence

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c. 3026G > A noted in our patient changes the neutral glycine residue to an acidic aspartate residue at position 1009 of the protein sequence (p.G1009D). This amino acid residue at position 1009 may play a vital role in maintaining the conformation of the catalytic site of *ADAR1* and a mutation at this locus may influence the normal function of the *ADAR1* enzyme.

The role of *ADAR1* mutation in the development of dyschromatosis symmetrica hereditaria is still unknown. One may speculate that the dysfunction of A-to-I editing induced by *ADAR1* mutation might affect differentiation of melanoblasts to melanocytes when melanoblasts migrate from the neural crest to the skin during development. Previous *in vitro* studies have indicated that *ADAR1* is related to viral inactivation,[3] so there is also a viewpoint that *ADAR1* mutation may increase susceptibility to viral infection and trigger apoptosis of melanocytes; this leads to the formation of hypopigmented lesions. Then the remnant melanocytes in the bulge area of hair follicles migrate toward the epidermis to form hyperpigmented macules.[2]

In our patient, typical lesions were observed on the elbows, knees, and buttocks other than dorsal extremities. The fact that typical lesions extended to the proximal extremity was also reported by Bilen *et al.*[4] and Kondo *et al.*[5] The variety of clinical phenotypes caused by mutation of the same gene suggests that other factors may influence the extent of the clinically apparent skin lesions.

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