GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

A novel insertion mutation in the *ADAR1* gene of a Chinese family with dyschromatosis symmetrica hereditaria

C.Y. Zhu*, K.J. Zhu*, Y. Zhou and Y.M. Fan

Department of Dermatology, Affiliated Hospital of Guangdong Medical College, Zhanjiang, Guangdong, China

*These authors contributed equally to this study.
Corresponding author: Y.M. Fan
E-mail: ymfan1963@163.com

Genet. Mol. Res. 12 (3): 2858-2862 (2013)
Received August 6, 2012
Accepted November 19, 2012
Published August 12, 2013
DOI http://dx.doi.org/10.4238/2013.August.12.1

ABSTRACT. Dyschromatosis symmetrica hereditaria (DSH) is an autosomal dominant pigmentary genodermatosis, characterized by a mixture of hyperpigmented and hypopigmented macules that are mainly present on the dorsal portions of the extremities. The DSH locus was mapped to chromosome 1q11-q12 and, subsequently, pathogenic mutations in the double-stranded RNA-specific adenosine deaminase (*ADAR1*) gene were identified. We performed a mutational analysis of the *ADAR1* gene in a Chinese family that included three individuals affected with typical DSH phenotypes. Mutations within the entire coding region and the exon-intron boundaries of *ADAR1* were detected and confirmed by polymerase chain reaction and direct sequencing, respectively. An insertion mutation within exon 12, c.3035_3036insC (p.P1012fsX1017), was identified in all family members affected by DSH, but not in the healthy members or 100 unrelated controls. This finding improves our understanding of the role of *ADAR1* in DSH.

Key words: Dyschromatosis symmetrica hereditaria; *ADAR1*; Mutation

INTRODUCTION

Dyschromatosis symmetrica hereditaria (DSH) [MIM#127400] is a pigmentary genodermatosis of autosomal dominant inheritance, characterized by a mixture of hyperpigmented and hypopigmented macules that are predominantly located on the dorsal regions of the limbs (Tomita and Suzuki, 2004). In a subset of DSH patients, small freckle-like pigmented macules also exist on the face (Li et al., 2010b). Ethnic background appears to be a major influence on the incidence of this disorder, as it is much more commonly found in Japanese and Chinese populations than in others (Oyama et al., 1999). By performing a genome-wide analysis of two large Chinese families, Zhang et al. (2003) mapped the gene responsible for DSH, double-stranded RNA-specific adenosine deaminase (*ADAR1*), to chromosome 1q11-q12. Subsequently, Miyamura et al. (2003) identified mutations in *ADAR1* in three families with DSH (Miyamura et al., 2003). *ADAR1* is composed of 15 exons that span approximately 30 kb on chromosome 1q21.3 (Miyamura et al., 2003; Zhang et al., 2003). The ADAR1 protein is responsible for the conversion of adenosine to inosine at specific locations within cellular RNAs (Mizrahi et al., 2012).

To better understand the pathogenic basis of heterozygous *ADAR1* mutations, we performed a mutational analysis of the *ADAR1* in one Chinese family containing members presenting typical DSH and, consequently, identified a novel insertion mutation in all affected persons. This mutation expands the database of known *ADAR1* mutations and may be helpful in the investigation of the still unknown mechanism of DSH.

MATERIAL AND METHODS

Subjects

Spanning three generations, members of a Chinese family with DSH and their healthy relatives were recruited from the Guangdong Province of China (Figure 1). Informed consent was obtained from all subjects that were included in clinical and genetic investigations and the study was approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical College. All DSH-affected individuals had typical hyperpigmented and hypopigmented macules on their extremities. The proband, individual III:1, was one 12-year-old boy. He presented asymptomatic hyperpigmented and hypopigmented macules on the dorsal portions of both hands and feet and has been developing freckle-like macules on his face since he was 5 months old (Figure 2). Histopathology revealed basal melanosis in the hyperpigmented macules. There was no familial history of skin cancer or other diseases.

Mutational analysis

Genomic DNA was extracted from the peripheral blood lymphocytes of 4 DSH patients, 6 of their healthy family members, and 100 unrelated healthy Chinese people. The DNA was then used to amplify the exons of *ADAR1* along with intronic flanking sequences by polymerase chain reaction (PCR) with previously described primers (Lai et al., 2012). PCR products were subsequently purified using a QIAquick PCR Purification kit (Qiagen, Germany), following which the *ADAR1* gene was sequenced with an ABI PRISM®3730 automated

sequencer (Applied Biosystems). Sequence comparisons and analyses were performed using the Phred-Phrap-Consed Version 12.0 program.

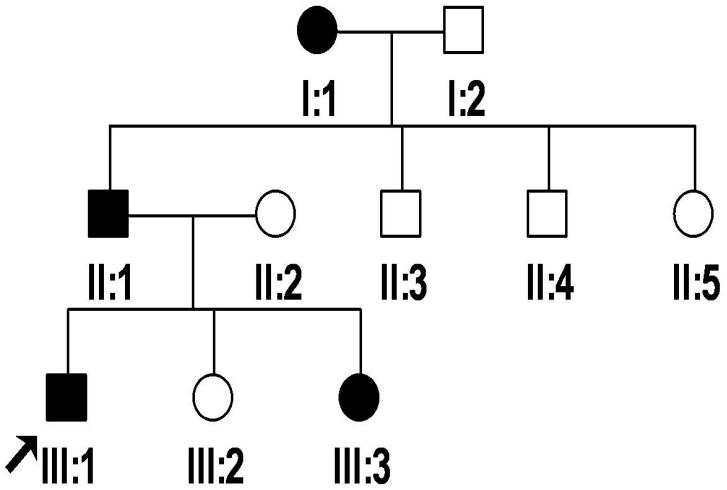

Figure 1. Pedigree of the dyschromatosis symmetrica hereditaria family studied.

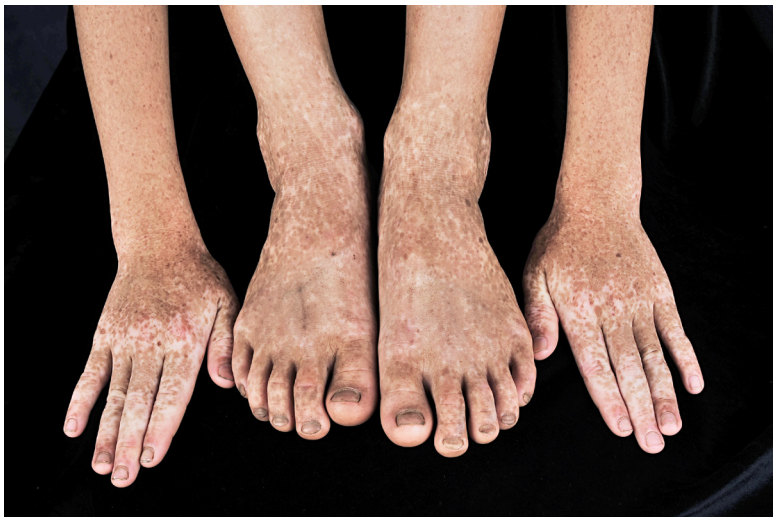

Figure 2. Small hyperpigmented and hypopigmented macules on the dorsal of both hands and feet in the proband.

RESULTS

The full results of the sequence analysis performed are shown in Figure 3. An insertion mutation in exon 12, c.3035_3036insC (p.P1012fsX1017), was identified in all DSH patients, but not in their healthy family members and in 100 unrelated healthy controls.

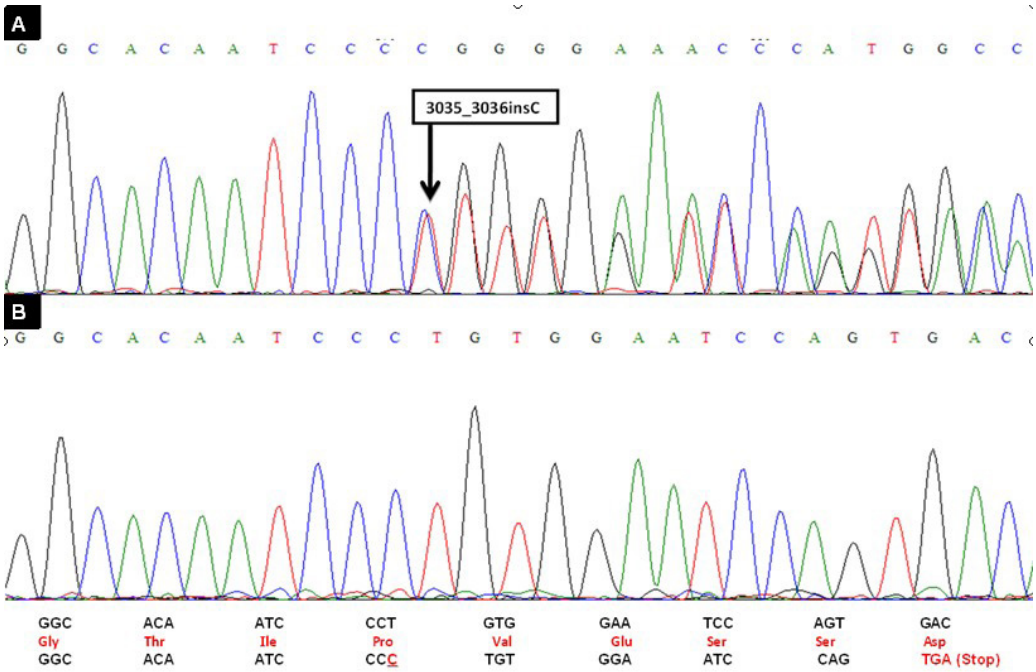

Figure 3. Mutation analysis of the double-stranded RNA specific adenosine deaminase (*ADAR1*) gene in the proband. **A.** Heterozygous c.3035_3036insC (p.P1012fsX1017) mutation in exon 12 of the *ADAR1* gene in proband. **B.** Sequence of exon 12 of the *ADAR1* gene in normal subjects.

DISCUSSION

DSH is a rare, autosomal dominant pigmentary genodermatosis associated with mutations in *ADAR1*, a gene that is expressed ubiquitously. The ADAR1 enzyme has two Z-alpha domains at exon 2, three double-stranded RNA binding domains at exons 2 to 7, and a putative deaminase domain (ADEAMc) corresponding to exons 9 to 14 (Li et al., 2010a). The deaminase domain, located in the codon from 886 to 1221 bp, represents approximately 27% of the length of the ADAR1 protein, (XuFeng et al., 2009). To date, over 130 unique *ADAR1* gene mutations have been detected, with more than 60% of those located within the ADEAMc domain (Bilen et al., 2012; Kantaputra et al., 2012; Kawaguchi et al., 2012; Lai et al., 2012; Luo et al., 2012; Mizrahi et al., 2012; Mohana et al., 2012; Shi et al., 2012), suggesting that the domain is a hot spot for mutations. The ADEAMc domain catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates to subsequently create alterative splicing sites or codon alterations, and thus ultimately leads to functional changes in proteins (Wagner et al., 1989; Rueter et al., 1999). In our study, the insertion mutation creates a stop codon. The mutation would theoretically halt ADAR1 protein synthesis before the full deaminase domain in exon 12 being translated, and causing the production of inactive ADAR1 enzymes.

In summary, we identified a novel mutation in the *ADAR1* involved in DSH pathogenesis. The newly discovered variant contributes to our understanding of *ADAR1* mutations in DSH.

ACKNOWLEDGMENTS

We are most grateful to the DSH patients and the members of their family for participating in this study. Research supported by the Guangdong Medical College Postdoctoral Fund (#XB1115) and the Guangdong Provincial Medical Research Fund (#B2010246 and #B2012282).

REFERENCES

Bilen N, Akturk AS, Kawaguchi M, Salman S, et al. (2012). Dyschromatosis symmetrica hereditaria: a case report from Turkey, a new association and a novel gene mutation. *J. Dermatol.* 39: 857-858.

Kantaputra PN, Chinadet W, Ohazama A and Kono M (2012). Dyschromatosis symmetrica hereditaria with long hair on the forearms, hypo/hyperpigmented hair, and dental anomalies: report of a novel *ADAR1* mutation. *Am. J. Med. Genet. A* 158A: 2258-2265.

Kawaguchi M, Hayashi M, Murata I, Hozumi Y, et al. (2012). Eleven novel mutations of the *ADAR1* gene in dyschromatosis symmetrica hereditaria. *J. Dermatol. Sci.* 66: 244-245.

Lai ML, Yang LJ, Zhu XH and Li M (2012). A novel mutation of the DSRAD gene in a Chinese family with dyschromatosis symmetrica hereditaria. *Genet. Mol. Res.* 11: 1731-1737.

Li CR, Xu XL, Sun XJ, Zong WK, et al. (2010a). Two new mutations of the *ADAR1* gene associated with dyschromatosis symmetrica hereditaria. *Arch. Dermatol. Res.* 302: 477-480.

Li M, Yang L, Li C, Jin C, et al. (2010b). Mutational spectrum of the *ADAR1* gene in dyschromatosis symmetrica hereditaria. *Arch. Dermatol. Res.* 302: 469-476.

Luo S, Zheng Y, Ni H, Liu Y, et al. (2012). Novel clinical and molecular findings in Chinese families with dyschromatosis symmetrica hereditaria. *J. Dermatol.* 39: 556-558.

Miyamura Y, Suzuki T, Kono M, Inagaki K, et al. (2003). Mutations of the RNA-specific adenosine deaminase gene (DSRAD) are involved in dyschromatosis symmetrica hereditaria. *Am. J. Hum. Genet.* 73: 693-699.

Mizrahi RA, Phelps KJ, Ching AY and Beal PA (2012). Nucleoside analog studies indicate mechanistic differences between RNA-editing adenosine deaminases. *Nucleic Acids Res.* 40: 9825-9835.

Mohana D, Verma U, Amar AJ and Choudhary RK (2012). Reticulate acropigmentation of dohi: a case report with insight into genodermatoses with mottled pigmentation. *Indian J. Dermatol.* 57: 42-44.

Oyama M, Shimizu H, Ohata Y, Tajima S, et al. (1999). Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): report of a Japanese family with the condition and a literature review of 185 cases. *Br. J. Dermatol.* 140: 491-496.

Rueter SM, Dawson TR and Emeson RB (1999). Regulation of alternative splicing by RNA editing. *Nature* 399: 75-80.

Shi BJ, Xue M, Liu Y, Jiang Y, et al. (2012). First report of the coexistence of dyschromatosis symmetrica hereditaria and psoriasis: one novel TCT to A mutation in the double-RNA-specific adenosine deaminase gene. *J. Eur. Acad. Dermatol. Venereol.* 26: 657-658.

Tomita Y and Suzuki T (2004). Genetics of pigmentary disorders. *Am. J. Med. Genet. C Semin. Med. Genet.* 131C: 75-81.

Wagner RW, Smith JE, Cooperman BS and Nishikura K (1989). A double-stranded RNA unwinding activity introduces structural alterations by means of adenosine to inosine conversions in mammalian cells and *Xenopus* eggs. *Proc. Natl. Acad. Sci. U. S. A.* 86: 2647-2651.

XuFeng R, Boyer MJ, Shen H, Li Y, et al. (2009). *ADAR1* is required for hematopoietic progenitor cell survival via RNA editing. *Proc. Natl. Acad. Sci. U. S. A.* 106: 17763-17768.

Zhang XJ, Gao M, Li M, Li M, et al. (2003). Identification of a locus for dyschromatosis symmetrica hereditaria at chromosome 1q11-1q21. *J. Invest. Dermatol.* 120: 776-780.

