Objective: To report and analyze the mutations of the double-stranded RNA-specific adenosine deaminase (DSRAD) gene in 2 Chinese pedigrees with dyschromatosis symmetrica hereditaria (DSH).

Design: Pedigree study.

Setting: Anhui province of China.

Patients: Two Chinese families, consisting of 19 individuals (family 1) and 5 individuals (family 2).

Interventions: We directly performed mutation detection of the DSARAD gene in 2 Chinese families with DSH by sequencing. The whole coding region of DSARAD was amplified by polymerase chain reaction, and products were analyzed by direct sequencing.

Main Outcome Measures: Frameshift DSARAD gene mutations.

Results: The c.3513insC (Arg1171fs) mutation was found in all patients but not in the healthy individuals from family 1, and the c.3220_3224delGCATC (Gly1073fs) mutation was found in 2 patients but not in the healthy members of family 2. These 2 mutations were not found in 96 unrelated control individuals.

Conclusion: Our data suggest that these 2 novel frameshift mutations in the DSARAD gene could cause DSH in the Chinese Han population and add new variants to the repertoire of DSARAD mutations in DSH.

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RNA–specific adenosine deaminase (DSRAD) gene responsible for DSH among Japanese families.

The DSRAD gene encodes the enzyme responsible for RNA editing by site-specific deamination of adenosines. The DSRAD protein catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates and induces translation within the nucleus, possibly at the surface of the nucleolus. We directly performed mutation detection of the DSRAD gene in 2 Chinese families with DSH by sequencing and found 2 mutations (c.3513insC and c.3220_3224delGCATC). These 2 frameshift mutations may lead to premature translation termination, and the truncated proteins with no functional activity can be synthesized.

METHODS

STUDY PARTICIPANTS

Two DSH families recruited for this study were identified through probands from Anhui province in a Chinese Han population. They showed an autosomal dominant inheritance pattern (Figure 1). Both families showed an autosomal dominant inheritance pattern. Family 1 consisted of 19 individuals and family 2 of 5 individuals. There were 8 affected individuals in family 1 and 2 affected individuals in family 2. The earliest onset of the disease in the 2 families was from ages 6 to 10 years. The proband of family 1, individual II:8, was a 40-year-old man with a long-standing history of both hypopigmented and hyperpigmented macules that presented diffusely on the extremities. In infancy, this individual developed pea-sized hyperpigmented and hypopigmented macules on the backs of his hands and feet (Figure 2). The results of laboratory examinations, including blood cell counts, blood chemical analysis, and urinalysis, were normal. Other affected members all had a mixture of hypopigmented and hyperpigmented macules of various sizes on the dorsal aspects of the extremities and no skin cancer history or other abnormalities. Some had small freckle-like pigmented macules on their faces, necks, and cheeks. The proband of family 2, individual II:2, was a 20-year-old woman who had been born following a normal pregnancy and delivery. At age 6 years, she developed a small mixture of hyperpigmented and hypopigmented macules on the backs of her hands and feet that ranged from 0.1 to 0.5 cm in diameter and gradually became prominent. In the summer or after sun exposure, the eruptions would become pronounced. Examination of the proband’s mother revealed diffuse hypopigmented and hyperpigmented macules on the backs of her hands and feet. Similar lesions in all affected individuals were seldom distributed on the skin of the trunk. These abnormalities are asymptomatic and do not affect general health.

IDENTIFICATION OF 2 FRAMESHIFT DSRAD GENE MUTATIONS

We found 2 frameshift mutations in our 2 Chinese families with DSH. The results of sequencing the PCR products from probands are shown in Figure 3. In the proband of family 1, the nucleotide C was inserted between the 3513 and 3514 nucleotide and formed the c.3513insC mutation. This mutation changes the reading frame of the DSRAD gene, leading to a premature stop codon (c.3513insC) and a truncated protein with no functional activity.

RESULTS

CLINICAL FINDINGS

A 3-generation family and a 2-generation family from Anhui province in China with typical DSH features were recruited (Figure 1). Both families showed an autosomal dominant inheritance pattern. Family 1 consisted of 19 individuals and family 2 of 5 individuals. There were 8 affected individuals in family 1 and 2 affected individuals in family 2. The earliest onset of the disease in the 2 families was from ages 6 to 10 years. The proband of family 1, individual II:8, was a 40-year-old man with a long-standing history of both hypopigmented and hyperpigmented macules that presented diffusely on the extremities. In infancy, this individual developed pea-sized hyperpigmented and hypopigmented macules on the backs of his hands and feet (Figure 2). The results of laboratory examinations, including blood cell counts, blood chemical analysis, and urinalysis, were normal. Other affected members all had a mixture of hypopigmented and hyperpigmented macules of various sizes on the dorsal aspects of the extremities and no skin cancer history or other abnormalities. Some had small freckle-like pigmented macules on their faces, necks, and cheeks. The proband of family 2, individual II:2, was a 20-year-old woman who had been born following a normal pregnancy and delivery. At age 6 years, she developed a small mixture of hyperpigmented and hypopigmented macules on the backs of her hands and feet that ranged from 0.1 to 0.5 cm in diameter and gradually became prominent. In the summer or after sun exposure, the eruptions would become pronounced. Examination of the proband’s mother revealed diffuse hypopigmented and hyperpigmented macules on the backs of her hands and feet. Similar lesions in all affected individuals were seldom distributed on the skin of the trunk. These abnormalities are asymptomatic and do not affect general health.
(Arg1171fs) mutation. This frameshift mutation was found within exon 15, confirmed in the other patients, and excluded in the remaining unaffected persons in family 1 (Figure 3A and B). Another frameshift mutation was found in exon 13 of the DSRAD gene in family 2. The 5 nucleotides GCATG were deleted from 3220 to 3224, which results in the mutation of c.3220_3224delGCATC (Gly1073fs) (Figure 3C and D). Sequencing of the PCR product from the proband’s mother in family 2 showed the same mutation as in her daughter. These 2 mutations were not detected in the 96 unrelated controls, suggesting that they are not common polymorphisms. These 2 mutations led to frameshift and premature translation termination within exon 15 and exon 13. The truncated proteins with no functional activity would be synthesized from the gene with these 2 frameshift mutations. We describe the amino acid position in DSRAD according to the sequence published on October 5, 2003 (GenBank accession No. 7669471; http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=7669471&db=Nucleotide&dopt=GenBank).

Dyschromatosis symmetrica hereditaria is a rare hereditary skin disease characterized by a mixture of hyperpigmented and hypopigmented macules of various sizes on the backs of the hands and feet. Variable and infrequent features reported with DSH include large, symmetric, hypopigmented vitiligo-like macules, which may be present around the eyes and mouth and on the knees and penis. This disease could also be associated with idiopathic torsion dystonia and idiopathic brain calcification. Oyama et al reviewed 185 DSH cases and reported that 77.6% of patients had a family history of these conditions and 22.4% had no family history. This finding is explained by sporadic cases based on spontaneous mutations or incomplete penetrance. Both DUH (OMIM 127500) and DSH are inherited pigmentary skin disorders. Clinically, DUH is difficult to differentiate from DSH; however, DUH skin lesions appear within the first month of life and predominantly on the trunk, whereas the age at onset of DSH is approximately 6 years, and the skin eruptions are mainly distributed on the extremities of the hands and feet. In this study, 2 DSH families were consistent with autosomal dominant inheritance, and skin eruptions occurred mainly on the dorsal aspects of the extremities. The patients developed typical skin lesions at approximately age 10 years. Apart from the skin lesions, there are no common associated disorders in these patients.
In the past 2 years, the studies about the molecular basis of DSH have improved. Our previous study\(^6\) mapped the first DSH gene locus on chromosome 1q11-1q21. The second locus, located at chromosome 6q24-2q6q25.2,\(^7\) was considered to be the DUh gene locus according to the clinical manifestations of the affected members. Miyamura et al\(^8\) confirmed this region and identified 4 heterozygous mutations of R474X (c.1420C→T), L923P (c.2768G→C), K952X (c.2854A→T), and F1165S (c.3494T→C) in the DSRAD gene among Japanese DSH families. Therefore, our group directly performed mutation detection of the DSRAD gene in 7 Chinese families and 2 sporadic cases of DSH by sequencing and tried to establish the genotype-phenotype correlations. Eight novel heterozygous mutations of DSRAD were identified: c.2433_2434delAG (T811fs→814X), c.2197G→T (E733X), c.3286C→T (R1096X), c.2897G→T (C966F), c.2797C→T (Q933X), c.2375delT (L792fs)\(^9\) et al speculated that when melanoblasts migrate from the root hair to the top of the feet, have a good prognosis.\(^23\) Miyamura et al\(^{10,11}\) showed that the c.3220_3224delGCATC (Gly1073fs) mutation in an irregular distribution in the skin lesions. Our studies showed that 2 mutations in exon 15 were detected, the frameshift mutation c.3513insC (Arg1171fs) and Phe1165Ser, but how to explain this finding is difficult because exon 15 is not involved in the catalytic domain. We suppose that these mutations will change the structure of the enzyme and may induce an unstable tertiary structure of the protein that results in defective activity.

In conclusion, in these 2 Chinese families, we detected 2 different and novel frameshift mutations of the DSRAD gene associated with DSH. The finding that different mutations of DSRAD could induce the same phenotype of DSH in different countries may give insight into the still unknown mechanism that leads to DSH.

REFERENCES


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