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A Novel Mutation of the ADAR1 Gene in a Chinese Family with Dyschromatosis Symmetrica Hereditaria and Literature Review

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Background: Dyschromatosis symmetrica hereditaria (DSH) is a rare genetic skin condition characterized by pigmented macules on the hands, feet, and sometimes the face. The ADAR1 gene is responsible for this autosomal dominant disorder.

Objective: This study aimed to analyze a three-generation Chinese family with DSH, identify a novel ADAR1 gene mutation, and conduct a comprehensive literature review of Chinese DSH families to enhance understanding of the genetic basis and clinical manifestations.

Methods: Clinical reports, mutation analysis, and literature reviews were conducted. A literature search was performed using PubMed.

Results: A novel heterozygous nonsense mutation, c.763C>T (p.Q255X), in the ADAR1 gene was identified in the proband and five other affected individuals. Literature review findings revealed prevalent mutation sites and clinical data in Chinese DSH families over the past two decades.

Limitations: The number of databases searched was limited, and the treatment outcomes for patients were not deemed satisfactory.

Conclusion: This study provides valuable insights into the genetic basis and clinical features of DSH in Chinese families, shedding light on prevalent mutation sites and clinical data. Further research is needed to explore the relationship between gene mutations and clinical phenotypes and advance therapeutic interventions for DSH.

Keywords: dyschromatosis symmetrica hereditaria, ADAR1 gene, mutation analysis

Introduction

Dyschromatosis symmetrica hereditaria (DSH: OMIM #127400, also called "reticulate acropigmentation of Dohi"), which is clinically characterized by a mixture of hyperpigmented and hypopigmented macules distributed on the dorsal aspects of their hands and feet. Some patients with DSH have freckle-like pigmented macules on the face. It is a rare autosomal dominant pigmentary genodermatosis with high penetrance. The skin lesions of this disease start in infancy or early childhood, cease spreading before adolescence, and persist throughout life. According to current literature, DSH is predominantly reported in Japan and China.[1] In 2003, Zhang et al[2] conducted gene detection on two Chinese DSH families and first identified the pathogenic gene for DSH located at chromosome 1q11-1q21. The gene responsible for DSH, known as the double-stranded RNA-specific adenosine deaminase (DSRAD) gene, has been located on chromosome 1q21.3 and comprises 15 exons. This gene is also referred to as the adenosine deaminase acting on RNA 1 (ADAR1) gene.[3]

Materials and Method

Ethical Approval

All procedures involving human participants were conducted in accordance with the ethical standards of the Ethics Committee of the Jinhua Municipal Central Hospital and the Helsinki Declaration. All patients, their normal family

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members, and 100 ethnically matched controls were informed about the purpose of the study and provided written consent prior to recruitment and sampling. Informed written consent for minors has been obtained from their legal guardians.

Clinical Report

In this study, we investigated a three-generation Chinese family with DSH (Figure 1a). All affected individuals had typical hyperpigmented and hypopigmented macules on the dorsal aspects of hands and feet. These skin lesions are irregular in shape and size, but they are asymptomatic. The cutaneous lesions of these patients are consistent with the typical clinical manifestations of DSH. The proband, individual III1, is a 31-year-old man. He developed an asymptomatic mixture of hyperpigmented and hypopigmented macules on dorsal aspects of his hands and feet at the age of 5. (Figure 1b and c) Besides the proband, there are five other affected individuals in the family. The other affected family members all have varying degrees of hyperpigmented and hypopigmented macules located on the dorsum of the hands and feet. Onset of symptoms occurred before the age of 6 for all affected individuals. It is worth noting that the proband in the family had the most severe skin lesions, which prompted a visit to our dermatology department for comprehensive genetic testing. Additionally, according to the patient and their family's description, there are no other related comorbidities in the family lineage. The family history conforms to an autosomal dominant inheritance pattern of hereditary symmetric dyschromatosis.

Mutation Analysis

After informed consent, genomic DNA was extracted from the peripheral blood of the proband and all family members. In addition, genomic DNA samples were extracted from 100 unrelated healthy volunteers as controls to exclude the possibility that these are polymorphisms in the ADAR1 gene. In our study, we designed primers that flanked all 15 coding exons and intron-exon boundaries of the ADAR1 gene using the Primer 3.0 program. The polymerase chain reaction was performed according to the method described in the previous literature.[4]

Results

A novel heterozygous nonsense mutation, c.763C>T (p.Q255X), located in exon 2 of the ADAR1 gene, was identified in the proband through direct sequence analysis of the PCR products. The same mutation was also detected in five other affected individuals in the family. This mutation was not found in other healthy family members or in 100 unrelated controls, indicating that c.763C>T is not a common polymorphism. A mutation occurs at the 763rd nucleotide in the DNA sequence of the ADAR1 gene, changing it from C to T. This resulted in the amino acid at position 255 in the protein sequence being altered from glutamine (Q) to a premature stop codon (X), causing premature termination of protein synthesis and the production of a truncated protein. (Figure 2).

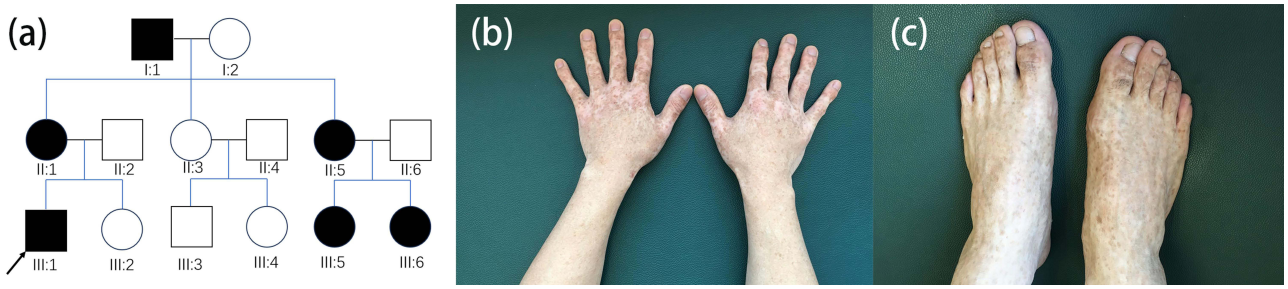

Figure 1 (**a**) Pedigree of the family: arrow indicates the proband. (**b** and **c**) A mixture of hyperpigmented and hypopigmented macules on the dorsal aspect of hands and feet in the proband.

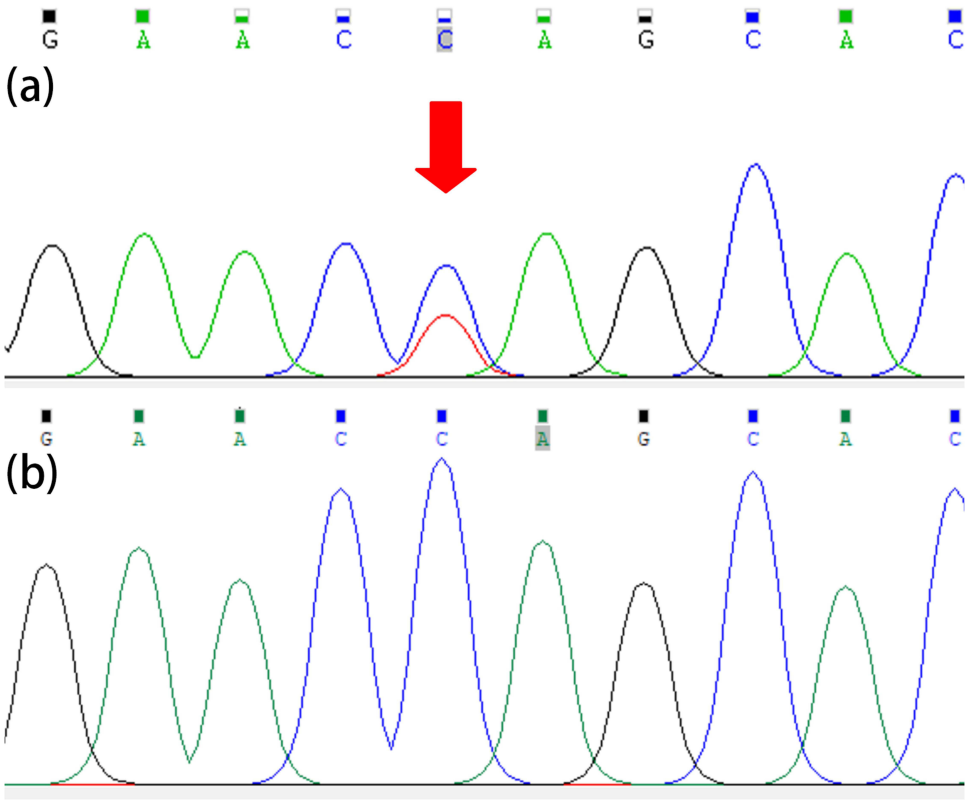

Figure 2 (**a**) A novel heterozygous nonsense mutation, c.763C>T (p.Q255X) mutation in exon 2 of the ADAR1 gene in proband. The red arrow indicates the mutation site. (**b**) The sequence of the exon 2 of the ADAR1 gene in normal individuals.

Literature Review

All the articles published in PubMed since 2003 were searched using the keywords of "dyschromatosis symmetrica hereditarian", "adenosine deaminase acting on RNA 1 gene", "ADAR1 gene", "double-stranded RNA-specific adenosine deaminase gene" and "DSRAD gene". Inclusion criteria: (1) diagnosed with DSH; (2) Chinese DSH pedigree; (3) Clinical manifestations, pedigree information and genetic testing are complete. (4) The full text is available. Exclusion criteria: (1) other ADAR gene-related diseases; (2) Non-Chinese pedigree; (3) incomplete clinical data; (4) outside the set time. Finally, 61 articles on Chinese DSH families were obtained through the above search criteria, involving 180 patients (Table 1). Ever since the identification of the pathogenic gene for DSH on chromosome 1q11-1q21 by Zhang et al in 2003, research on the detection of the ADAR gene has garnered significant attention. In this study, we conducted a review of genetic testing and clinical data pertaining to Chinese DSH families documented in the PubMed database over the past two decades. Remarkably, 86.1% of the patients exhibited a family history. Despite DSH being inherited as an autosomal dominant disorder, our cohort of 180 patients included 25 sporadic cases. According to the literature, almost all patients exhibited typical cutaneous manifestations on the dorsum of the hands and feet, which are crucial for clinical diagnosis. The face was identified as the second most common site, with some patients also presenting the macules on other areas such as the knees and elbows. Mutation analysis revealed that 36.1% (65/180) of the patients carried missense mutations, while frameshift mutations accounted for one-third of the cases (60/180) of the cases. Nonsense mutations were identified in 36 patients, and a small number of splice site mutations were also observed. Upon analyzing of the chromosomal locations where mutations occurred, we found 39 mutation sites located on chromosome 2, which may be considered as prominent mutation sites among Chinese families. (Figure 3) This paper presents a compilation of Chinese DSH families over the past 20 years, along with a summary of prevalent mutation sites and clinical manifestations, aiming to facilitate future investigations into the relationship between gene mutations and clinical phenotypes.

Table 1 ADAR1 Mutation Spectrum in Chinese Patients with DSH

No.*	Patient's pedigree	Phenotype		Mutation				Reference
	Incidence	Age of onset (proband)	Lesion distribution (proband)	Position	Nucleotide change	Amino acid change	Mutation type	
1	Familial	Within 12 m	Back of hands and feet, elbow, knees	Exon2	c.1096_1097del	p.K366fsX	Frame-shift	Liu et al 2023[5]
2	Familial	Within 12 m	/	Exon2	c.518A>G	p.N173S	Missense	
3	Familial	8y	Back of hands and feet	Exon2	c.511G>T	p.E171*	Nonsense	Ma et al 2023[6]
4	Familial	3y	Back of hands and feet, face	Exon14	c.3385T>G	p.C1129G	Missense	
5	Familial	3y	Back of hands and feet, face	Exon14	c.3384G>C	p.W1128C	Missense	
6	Familial	3y	Back of hands and feet	Exon2	c.716G>A	p.R239Q	Missense	
7	Sporadic	/	Back of hands and feet	Intron6	c.2080–1G>T	/	Splice-site	
8	Familial	At birth	Back of hands and feet, face	Exon12	c.3358–3359insT	p.L1053fs-1092X	Frame-shift	Ning et al 2022[4]
9	Familial	2y	Back of hands and feet	Exon15	c.3820–3821insG	p.G1207fs-1213X	Frame-shift	
10	Familial	5y	Back of hands and feet, face	Exon3	c.1622T>A	p.I541N	Missense	Liu et al 2022[7]
11	Familial	/	Back of hands	Exon15	c.3556A>G	p.K1186E	Missense	Weng et al 2021[8]
12	Sporadic	/	Back of hands and feet	Exon11	c.2941_2942insAT	p.M981IfsTer74	Frame-shift	
13	Familial	Median age was 2.6y	/	Exon3	c.1760A>G	p.Y587C	Missense	Liu et al 2021[9]
14	Familial			IVS8	c.2669–2A>G	/	splice-3	
15	Familial			IVS11	c.3020–2A>G	/	splice-3	
16	Familial			Exon9	c.2762G>A	p.R921K	Missense	
17	Familial			Exon12	c.3140delG	p.G1047Afs*7f	Frame-shift	
18	Familial			Exon13	c.3286C>T	p.R1096*	Nonsense	
19	Familial			Exon8	c.2658C>G	p.S886R	Missense	
20	Familial			Exon3	c.1600C>T	p.R534*	Nonsense	
21	Familial			Exon7	c.2433_2434delAG	p.A813Qfs*29	Frame-shift	
22	Familial			Exon2	c.792_805delinsATCTTAC	p.S264Rfs*29	Coding DNA sequence(CDS)-indel	
23	Familial			Exon3	c.1600C>T	p.R534*	Nonsense	
24	Familial			Exon3	c.1630C>T	p.R544*	Nonsense	

25	Familial	1y	Back of hands and feet	Exon2	c.497delA	p.R105fs	Frame-shift	Wang et al 2019[10]
26	Familial	8m	Back of hands and feet	Exon12	c.3352C>T	p.Q1058*	Nonsense	
27	Familial	2y	Back of hands and feet, ankle	Exon15	c.3722delT	p.S1181fs	Frame-shift	
28	Familial	2y	Back of hands and feet	Exon2	c.1330A>G	p.V332M	Missense	
29	Familial	1y	Back of hands and feet	Exon8	c.2702A>T	p.H841L	Missense	
30	Familial	4y	Back of hands and feet	Exon2	c.1176G>A	p.K326E	Missense	
31	Familial	10m	Back of hands and feet	Exon9	c.2861G>A	p.R892H	Missense	
32	Familial	/	Back of hands and feet	Exon9	c.2722G>T	p.D908Y	Missense	Hu et al, 2019[11]
33	Familial	/	Back of hands and feet	Exon10	c.2865_2866delGT	p.V955fs	Frame-shift	
34	Familial	/	Back of hands and feet	Exon3	c.1657delA	p.S553fs	Frame-shift	
35	Familial	/	Back of hands and feet	Exon14	c.3363_3364insT	p.K1122fs	Frame-shift	
36	Sporadic	/	Back of hands and feet	Exon8	c.2563_2564delCT	p.L855fs	Frame-shift	
37	Sporadic	/	Back of hands and feet	Exon2	c.526T>G	p.L176V	Missense	
38	Sporadic	/	Back of hands and feet	Exon3	c.1630C>T	p.R544X	Nonsense	
39	Sporadic	/	Back of hands and feet	Exon11	c.2894C>T	p.P965L	Missense	
40	Familial	/	Back of hands and feet	Exon12	c.3155T>C	p.L1052P	Missense	Liu et al 2017[12]
41	Familial	3y	Back of hands and feet	Exon13	c.3233G>A	p.R1078H	Missense	Tang et al 2018[13]
42	Familial	3y	Back of hands and feet, face	Exon13	c.3286C>T	p.R1096*	Nonsense	
43	Familial	3y	Back of hands and feet	Intron11	c.3019+1G>T	Unknown	Splice-site	
44	Familial	1y	Back of hands and feet, face	Exon11	c.2894C>A	p.Pro965Q	Missense	
45	Familial	2y	Back of hands and feet	Exon2	c.1202_1205del	p.N401fs	Frame-shift	
46	Familial	2y	Back of hands and feet	Exon7	c.2280C>A	p.Y760*	Nonsense	
47	Familial	6y	Back of hands and feet, face	Intron4	c.1934+3A>G	Unknown	Splice-site	
48	Familial	2y	Back of hands and feet	Exon3	c.1615del	p.V539fs	Frame-shift	
49	Familial	6y	Back of hands and feet	Exon9	c.2749A>G	p.R917G	Missense	
50	Familial	10y	Back of hands and feet	Exon2	c.1371_1372insCCACAGAT	p.D458fs	Frame-shift	
51	Familial	2y	Back of hands and feet, face	Intron13	c.3315+1G>A	/	Splice-site	
52	Familial	3y	Back of hands and feet	Exon7	c.2433_2434del	p.T811fs	Frame-shift	
53	Familial	1m	Back of hands and feet, knees	Exon7	c.2310_2311insA	p.A771fs	Frame-shift	
54	Familial	6y	Back of hands and feet	Exon2	c.1068dupA	p.D357RfsX18	Frame-shift	Chi et al 2017[14]
55	Familial	6y	Back of hands and feet, face	Exon13	c.3233G>T	p.R1078P	Missense	Zhang et al 2017[15]
56	Familial	At birth	Back of hands and feet	Exon15	c.3576C>G	p.Y1192X	Nonsense	Zhou et al[16] 2017
57	Familial	At birth	Back of hands and feet, face	Exon4	c.1912delG	p.E673VfsX652	Frame-shift	
58	Familial	5m	Back of hands and feet, face	Exon6	c.2253insG	p.G751fs	Frame-shift	Li et al 2016[17]

(*Continued*)

Table 1 (Continued).

No.*	Patient's pedigree	Phenotype		Mutation				Reference
	Incidence	Age of onset (proband)	Lesion distribution (proband)	Position	Nucleotide change	Amino acid change	Mutation type	
59	Familial	3 to 15 years	Back of hands and feet	Exon12	c.3089_3090delGA	p.R1030DfsX1036	Frame-shift	Zhang et al 2016[18]
60	Familial		Back of hands and feet, face	Exon15	c.3679T>C	p.Stop1227R	Nonstop	
61	Familial		Back of hands and feet, face	Exon7	c.2408delG	p.G803VfsX807	Frame-shift	
62	Familial		Back of hands and feet	Exon2	c.1078C>T	p.R360X	Nonsense	
63	Familial		Back of hands and feet, face	Exon14	c.3439ins17	p.D1147VfsX1184	Frame-shift	
64	Familial		Back of hands and feet	Exon2	c.1420C>T	p.R474X	Nonsense	
65	Familial	7y	Back of hands and feet	Exon13	c.3248G>A	p.R1083H	Missense	
66	Sporadic	3 to 15 years	Back of hands and feet, face	Exon7	c.2303G>A	p.W768X	Nonsense	
67	Sporadic		Back of hands and feet, face	/	/	/	/	
68	Familial	2y	Back of hands and feet, trunk, thigh, button	Exon2	c.1325C>G	p.S442Ter	Nonsense	Liu et al 2016[19]
69	Familial	About 6m	Back of hands and feet, elbows, knees, buttocks	Exon12	c.3026G>A	p.G1009D	Missense	Li et al 2015[20]
70	Familial	1y	Back of hands and feet	Exon8	c.2633_2634delCT	p.S878fs	Frame-shift	Xu et al 2015[21]
71	Familial	Childhood	Back of hands and feet	Exon2	c.1057_1058delTG	p.W353fs	Frame-shift	
72	Sporadic	/	Back of hands and feet	Exon8	c.2563–2566delCTGA	p.L855fs	Frame-shift	Li et al 2014[22]
73	Familial	3 to 10 years	Back of hands and feet	Exon2	c.556C>T	p.Q186X	Nonsense	Liu et al 2014[23]
74	Familial		Back of hands and feet	Exon11	c.3001C>T	p.R1001Cys	Missense	
75	Familial		Back of hands and feet, ankles	Exon5	c.1936_1937insTG	p.F646LfsX16	Frame-shift	
76	Familial		Back of hands and feet, face	Exon2	c.1065_1068delGACA	p.D357RfsX47	Frame-shift	
77	Familial		Back of hands and feet, face	Exon2	c.1601G>A	p.G471DfsX30	Splicing	
78	Familial		Back of hands and feet	Exon9	c.2744C>T	p.S915F	Missense	
79	Familial		Back of hands and feet	Exon15	c.3463C>T	p.R1155W	Missense	
80	Familial	7y	Back of hands and feet, elbows, knees	Exon2	c.1479C>G	p.Y493X	Nonsense	Wu et al 2014[24]
81	Familial	1y	Back of hands and feet	Exon12	c.3140G>A	p.G1047D	Missense	Zhang et al 2013[25]
82	Familial	2y	Back of hands and feet	Exon3	c.1760A>G	p.Y587C	Missense	
83	Familial	/	Back of hands and feet	Exon10	c.2857A>T	p.K953X	Nonsense	Huang et al 2014[26]
84	Familial	5m	Back of hands and feet, face	Exon12	c.3035_3036insC	p.P1012fsX1017	Frame-shift	Zhu et al 2013[27]
85	Familial	5y	Back of hands and feet	Exon2	c.271_272delAG	p.R91fsX123	Frame-shift	Zhang et al 2013[28]
86	Familial	5y	Back of hands and feet	Exon6	c.2099–2100delAG	p.E700fsX702	Frame-shift	Zhang et al 2013[29]
87	Familial	6y	Back of hands and feet, face	Exon2	c.1420C>T	p.R474X	Nonsense	

88	Sporadic	1y	Back of hands and feet	Exon15	c.3463C>T	p.R1155W	Missense	Yuan et al 2012[30]
89	Sporadic	1y	Back of hands and feet	Exon15	c.3463C>T	p.R1155W	Missense	
90	Sporadic	2y	Back of hands and feet, ankles	Exon3	c.1605delT	p.F535fs	Frame-shift	
91	Sporadic	3y	Back of hands and feet, face, neck	Exon3	c.1630C>T	p.R544X	Nonsense	
92	Familial	5y	Back of hands and feet	Exon11	c.3002G>T	p.R1001L	Missense	Lai et al 2012[31]
93	Familial	28y	Back of hands	Exon2	c.1470T>A	p.C490X	Nonsense	Luo et al 2011[32]
94	Familial	/	Back of hands and feet	Exon2	c.1156A>G	p.N386D	Missense	
95	Familial	/	/	Exon15	c.3483T>A	p.I1161M	Missense	
96	Familial	/	/	Exon3	c.1615delG	p.V539fs	Frame-shift	Liu et al 2011[33]
97	Familial	/	/	Exon2	c.ins1372-9CCACAGAT	p.D458fs	Frame-shift	
98	Familial	/	Back of hands and feet	Intron10	IVS10-5T>C	/	Splice-site	Liu et al 2011[34]
99	Familial	/	Back of hands and feet	Intron11	IVS11-2G>A	/	Splice-site	
100	Familial	3y	Back of hands and feet	Exon8	c.2632T>A, c.2633_2634delCT	p.S878fs	Missense, Frame-shift	Shi et al 2011[35]
101	Familial	4y	Back of hands and feet, face	Intron6	IVS6-3A>G	/	Splice-site	Wang et al 2010[36]
102	Familial	6y	Back of hands and feet, face	Intron12	IVS12+5G>A	/	Splice-site	
103	Familial	/	Back of hands and feet, face	Exon2	c.767delA	p.H256fs260X	Frame-shift	Pan et al 2010[37]
104	Familial	14y	Back of hands and feet	Exon5	c.1990_1991delAGinsC	p.S664fsX677	insertion–deletion(indel), Frame-shift	Li et al 2010[38]
105	Familial	2y	Back of hands and feet	Exon13	c.3286C>T	p.R1096X	Nonsense	Wang et al 2010[39]
106	Familial	About 2y	Back of hands and feet	Exon13	c.3247C>T	p.R1083C	Missense	
107	Sporadic	Childhood	Back of hands and feet	Exon11	c.2894C>T	P965L	Missense	
108	Familial	4y	Back of hands and feet	Exon2	c.1018C>T	p.Q340X	Nonsense	
109	Familial	Childhood	Back of hands and feet	Exon2	c.1072A>T	p.K358X	Nonsense	
110	Sporadic	3y	Back of hands and feet	Exon14	c.3419A>G	p.D1140G	Missense	
111	Familial	6y	Back of hands and feet	Exon8	c.2858C>G	p.S886R	Missense	Dong et al 2011[40]
112	Sporadic	3y	Back of hands and feet, face	Intron5	c.2080–1G>A, IVS5-1G>A	/	Splice-site	Li et al 2010[41]
113	Familial	7y	Back of hands and feet, face	Exon12	c.3076C>T	p.R1026W	Missense	

(*Continued*)

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Table 1 (Continued).

No.*	Patient's pedigree	Phenotype		Mutation				Reference
	Incidence	Age of onset (proband)	Lesion distribution (proband)	Position	Nucleotide change	Amino acid change	Mutation type	
114	Familial	6 months to 17 years	Back of hands and feet	Exon9	c.2747G>A	p.R916Q	Missense	Li et al 2010[42]
115	Familial		Back of hands and feet, neck	Exon13	c.3209insC	p.L1070fsX1092	Frame-shift	
116	Familial		Back of hands and feet, forearms	Exon9	c.2747G>A	p.R916Q	Missense	
117	Familial		Back of hands and feet	Exon9	c.2742delC	p.I914fsX927	Frame-shift	
118	Familial		Back of hands and feet, neck, knees	Exon12	c.3159delG	p.L1053fsX1076	Frame-shift	
119	Familial		Back of hands and feet, ankles	Exon2	c.615insA	p.N205fsX217	Frame-shift	
120	Familial		Back of hands and feet, face	Exon15	c.3574T>G	p.Y1192D	Missense	
121	Familial		Back of hands and feet, forearms	Exon2	c.633insT	p.V211fsX217	Frame-shift	
122	Familial		Back of hands and feet, face	Exon2	c.1420C>T	p.R474X	Nonsense	
123	Familial		Back of hands and feet	Exon13	c.3286C>T	p.R1096X	Nonsense	
124	Familial		Back of hands and feet, forearms	Exon15	c.3463C>T	p.R1155W	Missense	
125	Familial		Back of hands and feet	/	/	/	/	
126	Sporadic		Back of hands and feet, ankles	Exon2	c.1211delT	p.V404fsX417	Frame-shift	
127	Sporadic		Back of hands and feet, neck	Exon2	c.77G>A	p.R26K	Missense	
128	Familial	/	/	Exon9	c.G2747A	p.R916Q	Missense	Xu et al 2010[43]
129	Familial	/	/	Exon12	c.C3124T	p.R1042C	Missense	
130	Familial	At birth	Back of hands and feet, fingers, toes	Exon10	c.3073A>G	p.H958R	Missense	Dong et al 2009[44]
131	Familial	8y	Back of hands and feet, knees	Exon15	c.3617T>C	p.M1206T	Missense	Li et al 2008[45]
132	Familial	6y	Back of hands and feet	Exon3	c.1614_1620insAATTCCA	p.Q538fsX552	Frame-shift	Ren et al 2008[46]
133	Sporadic	/	Back of hands and feet, face	Exon13	c.3315G>T	p.K1105N	Missense	Zhang et al 2008[47]
134	Familial	/	Back of hands and feet, face, calves, knees	Exon12	c.3139G>C	p.G1047R	Missense	
135	Familial	/	Back of hands and feet, face	Exon13	c.3286C>T	p.R1096x	Nonsense	
136	Familial	/	Back of hands and feet, face, neck	Exon7	c.2337delA	p.Q779fs	Frame-shift	
137	Familial	/	Back of hands and feet, face, forearms	Exon2	c.1323delC	p.P441fs	Frame-shift	
138	Familial	/	Back of hands and feet	Exon13	c.3295T>C	p.F1099L	Missense	
139	Familial	/	Back of hands and feet forearms	Exon12	c.3202G>C	p.G1068R	Missense	
140	Familial	/	Back of hands and feet, face, neck	/	/	/	/	
141	Familial	/	Back of hands and feet, face, knees, ankles	/	/	/	/	
142	Familial	10y	Back of hands and feet, face, neck, forearms	Exon12	c.3125G>A	p.R1042H	Missense	Li et al 2007[48]
143	Familial	6y	Back of hands and feet, face	Exon2	c.941_942delCT	p.314fs319X	Frame-shift	Xing et al 2007[49]

144	Familial	3 months to 8 years	Back of hands and feet	Exon13	c.3286C>T	p.R1096X	Nonsense	Hou et al 2007[50]
145	Familial		Back of hands and feet	Exon2	c.1491insA	p.T497fs516X	Frame-shift	
146	Familial		Back of hands and feet	Exon8	c.2568–2571delTAAC	p.T856fs	Frame-shift	
147	Familial		Back of hands and feet	Exon13	c.3247C>T	p.R1083C	Missense	
148	Familial		Back of hands and feet	Intron12	c.3203–2A>G	/	Splice-site	
149	Sporadic		Back of hands and feet	Exon2	c.982C>T	p.R328X	Nonsense	
150	Sporadic		Back of hands and feet	Exon12	c.3040G>T	p.E1014X	Nonsense	
151	Sporadic		Back of hands and feet	Exon11	c.2969C>G	p.P990R	Missense	
152	Familial	8y	Back of hands and feet	Exon9	c.2747G>T	p.R916L	Missense	Liu et al 2006[51]
153	Familial	/	Back of her hands and feet, face, wrists, ankles	Exon6	c.2116G>A	p.E706K	Missense	Lu et al 2006[52]
154	Familial	6m	Back of hands and feet, wrists, forearms	Exon10	c.2848C>T	p.Q950X	Nonsense	
155	Familial	2y	Back of hands and feet, face	Exon8	c.2565_2568delGACT	p.L855fs	Frame-shift	Liu et al 2006[53]
156	Familial	14y	Back of hands and feet	Exon7	c.2433_2434delAG	p.T811fs	Frame-shift	
157	Familial	3 to 12 years old	/	/	c.1555delT	p.C519fs	Frame-shift	Liu et al 2006[54]
158	Familial		/	/	c.3116A>G	p.K1039R	Missense	
159	Sporadic	1y	Back of hands and feet, knees	Exon8	c.2645delG	p.G882fsX901	Frame-shift	Chao et al 2005[55]
160	Familial	1 to 6 years old	Back of the extremities, face, elbow, knee joints	Exon13	c.3244A>G	p.H1075R	Missense	Li et al[56] 2005
161	Familial	6y	Back of hands and feet	Exon14	c.3335_3336delAT	p.Y1112fsfi1112X	Frame-shift	
162	Familial	6y	Back of hands and feet, wrists, ankles	Exon11	c.2929delA	p.S977A	Frame-shift	Xing et al 2005[57]
163	Familial	6 to 9 years old	Back of hands and feet, face	Exon2	c.1420C>T	p.R474X	nonsense	Sun et al 2005[58]
164	Familial		Back of hands and feet, face	Exon12	c.3169delC	p.L1057fs	Frame-shift	
165	Familial		Back of hands and feet, face	Exon13	c.3247C>T	p.R1083C	Missense	
166	Familial	3y	Back of the hands, wrists, forearms	Exon14	c.3388T>C	p.C1130R	Missense	Cui et al 2005[59]
167	Familial	6 to 10 years old	Back of the hands and feet	Exon15	c.3513insC	p.R1171fs	Frame-shift	Gao et al 2005[60]
168	Familial	6y	Back of the hands and feet	Exon13	c.3220_3224delGCATC	p.G1073fs	Frame-shift	
169	Familial	6y	Back of the hands and feet, heels	Exon15	c.3463C>T	p.R1155W	Missense	Li et al 2005[61]
170	Familial	/	Back of the hands and feet	Exon10	c.2879A>G	p.Y960C	Missense	Li et al 2004[62]

(*Continued*)

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Table 1 (Continued).

No.*	Patient's pedigree	Phenotype		Mutation				Reference
	Incidence	Age of onset (proband)	Lesion distribution (proband)	Position	Nucleotide change	Amino acid change	Mutation type	
171	Familial	4 to 10 years old	/	Exon7	c.2433_2434delAG	p.T811fs841X	Frame-shift	Zhang et al 2004[63]
172	Familial	4 to 9 years old		Exon6	c.2197G>T	p.E733X	Nonsense	
173	Familial	8 months to 9 years old		Exon13	c.3286C>T	p.R1096X	Nonsense	
174	Familial	3 to 11 years old		Exon13	c.3286C>T	p.R1096X	Nonsense	
175	Familial	4 to 15 years old		Exon11	c.2897G>T	p.C966F	Missense	
176	Familial	6 months to 6 years old		Exon10	c.2797C>T	p.Q933X	Nonsense	
177	Sporadic	10y		Exon7	c.2375delT	p.L792fs792X	Frame-shift	
178	Sporadic	8y		Intron12	c.3032–2A>G	/	Splice acceptor	
179	Familial	7y	Back of her hands and feet, face, wrists, ankles	Exon2	c.1537C>T	p.Q513X	Nonsense	Liu et al 2004[64]
180	Familial	3y	Back of her hands and feet, face, elbow, knee joints	Exon9	c.2746C>T	p.R916W	Missense	

Note: *: Patient Number; y: years old; m: months.

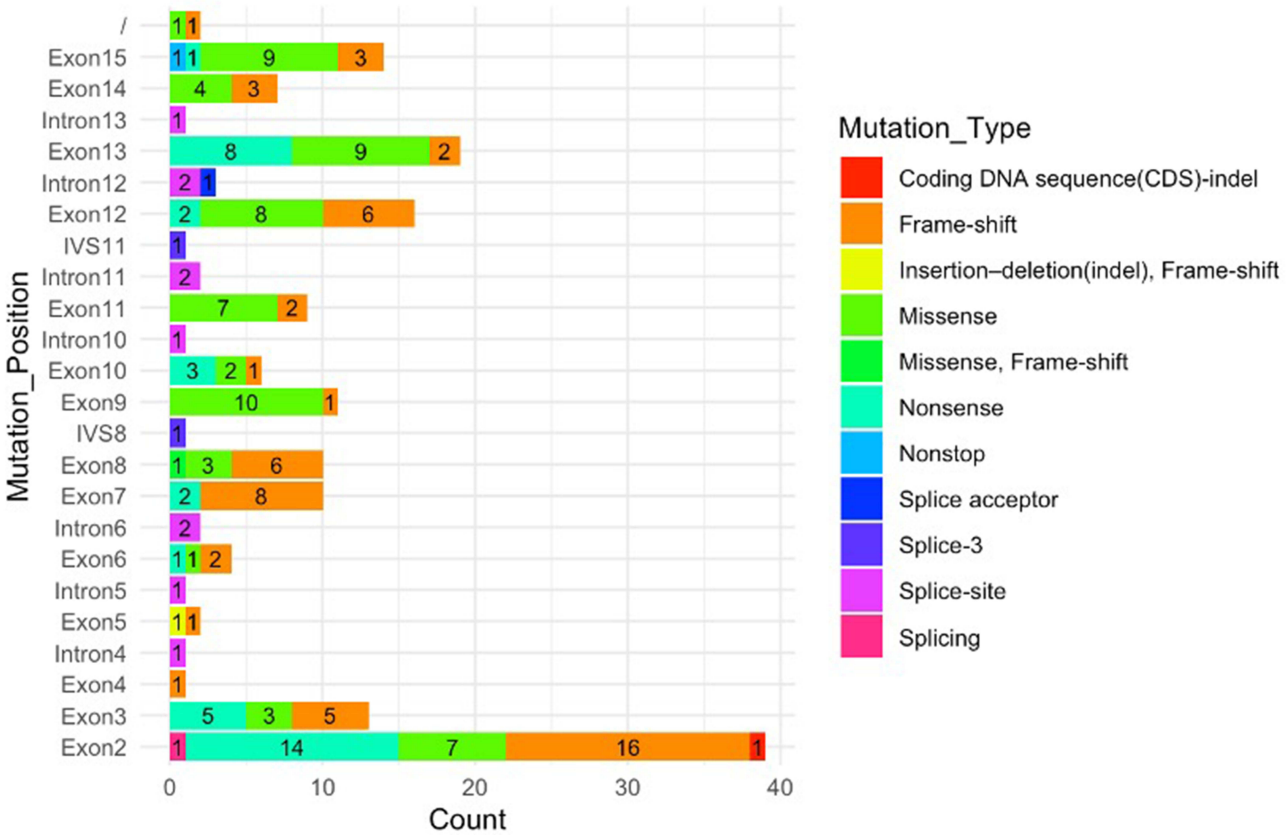

Figure 3 The relation of mutation position and mutation type.

Discussion

ADAR1 protein as an A-to-I editase, catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates.[65] ADAR1 has two different isoforms: ADAR1p110 and ADAR1p150. The p150 isoform has two series of Z-DNA-binding domains (Z-α and Z-β) located in exon 2, three dsRNA-binding domains (DSRM) located in exons 2–7 and a deaminase domain (ADEAMc) located in exons 9–14. In contrast, The P110 isoform has only one Z-DNA binding domain(Z-β) located in exon 2.[15,66] To date, there is no etiologic treatment for DSH. Sun exposure exacerbates hyperpigmentation and hypopigmented macules in individuals with DSH, particularly in exposed areas such as the dorsal aspects of the hands. This can lead to significant psychosocial stress, especially among young patients. Consequently, proactive sun protection measures are effective and recommended for all individuals affected by this condition.[67] Kawakami et al[68] achieved successful treatment of a male patient in Japan through the use of 1-mm miniature punch grafting in combination with 308-nm excimer light. Many patients, including the subject of this study, expressed a strong desire for treatment. To address the skin hyperpigmentation of the patients, fractional CO2 laser, 532-nm Q-switched Nd: YAG Laser, and 694nm Q-switched ruby laser were successively employed. Meanwhile, at the site of pigmentation reduction, the 308-nm excimer laser was utilized to help restore pigment deposition. Initial observations indicated a resolution of the pigment differences within weeks following the conclusion of the treatment. However, despite multiple attempts over several months, the lesions eventually reverted to their pre-treatment state, yielding unsatisfactory results. In conclusion, this study unveiled a novel heterozygous nonsense mutation, c.763C>T (p.Q255X), within the ADAR1 gene in a multi-generational Chinese family affected by dyschromatosis symmetrica hereditaria (DSH). Simultaneously, pigment augmentation treatment was administered to the hypopigmented areas of the patient, and pigment reduction treatment was applied to the hyperpigmented areas. However, no significant improvement was observed in either case. Through an extensive review of Chinese DSH families spanning the last two decades, the study illuminated prevalent mutation sites and clinical manifestations, significantly augmenting our comprehension of the genetic underpinnings

and clinical characteristics of DSH within Chinese communities. Moving forward, these insights are poised to inform future investigations into the interplay between gene mutations and clinical phenotypes in DSH, potentially paving the way for advancements in therapeutic interventions and management strategies for this condition.

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Disclosure

Authors declare no conflict of interests for this article.

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