—Case Reports—

An *ATP2A2* Missense Mutation in a Japanese Family with Darier Disease: A Case Report and Review of the Japanese Darier Disease Patients with *ATP2A2* Mutations

Min Li[1], Naoyuki Higashi[1], Hajime Nakano[2] and Hidehisa Saeki[3]

[1]Department of Dermatology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[2]Department of Dermatology, Hirosaki University Graduate School of Medicine, Aomori, Japan
[3]Department of Dermatology, Nippon Medical School Hospital, Tokyo, Japan

Darier disease (DD) is a rare autosomal dominant skin disorder due to mutations in the *ATP2A2* gene, which encodes sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2). The clinical manifestations of DD are characterized by warty papules and plaques in seborrheic areas, and association with neuropsychiatric abnormalities has also been reported in a few families with DD. We herein report a classic Japanese DD case with a previously described mutation (p.C560R) in *ATP2A2*. In Japan, 26 mutations in the *ATP2A2* gene in 7 pedigrees and 19 sporadic cases with DD have been reported, among which one pedigree and one sporadic case were accompanied by neuropsychiatric symptoms. A review of the reports confirmed that most mutations were of the missense type and no consistent genotype-phenotype correlations were found. (J Nippon Med Sch 2017; 84: 246–250)

Key words: Darier disease, *ATP2A2* mutation

Introduction

Darier disease (DD), first described by Darier and White in 1889, is a rare autosomal dominant skin disorder characterized by warty papules and plaques in seborrheic areas (central trunk, flexures, scalp and forehead)[1]. Other clinical features include palmo-plantar pits, nail changes, and association with neuropsychiatric abnormalities such as mild mental retardation and epilepsy has also been reported in a few families with DD[1]. The penetration of the disease is complete and the age of onset is typically within the second decade. Mutations in the *ATP2A2* gene are the cause of DD[2]. This gene is located on chromosome 12q23-24.1 and encodes the sarco/endoplasmic reticulum Ca^{2+} ATPase isoform 2 (SERCA2), a calcium pump transporting Ca^{2+} from the cytoplasm into the ER lumen[2]. Herein, we report a typical Japanese DD patient with a mutation in *ATP2A2* that has been previously described and review the reported Japanese DD cases with *ATP2A2* mutations.

Case

A 34-year-old woman presented with a severe pruritic skin eruption on her neck and trunk. Her skin lesions, diagnosed as folliculitis, were mild 10 years ago, but became exacerbated 1 year ago after catching a cold. Physical examination revealed multiple slightly crusted brownish-red keratotic papules and plaques on the neck and trunk (**Fig. 1A and B**). Nail lesions with V-shaped notches on the distal end of the nail plate were also seen (**Fig. 1C**). She had no history of neuropsychiatric abnormalities. A skin biopsy taken from her back revealed suprabasal acantholysis in the epidermis with dyskeratotic cells (known as corps ronds and grains) (**Fig. 2A and B**). These clinical and histological findings were consistent with the diagnosis of DD. After obtaining informed consent, genomic DNA was extracted from the peripheral blood leukocytes and all 21 exons of the *ATP2A2* gene, including intron-exon boundaries, were amplified by polymerase chain reaction as described previously[3]. Direct sequencing revealed a heterozygous missense mutation in exon 13, c.1678T>C, resulting in the amino acid

Correspondence to Min Li, MD, Department of Dermatology, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: limin@nms.ac.jp
Journal Website (http://www2.nms.ac.jp/jnms/)

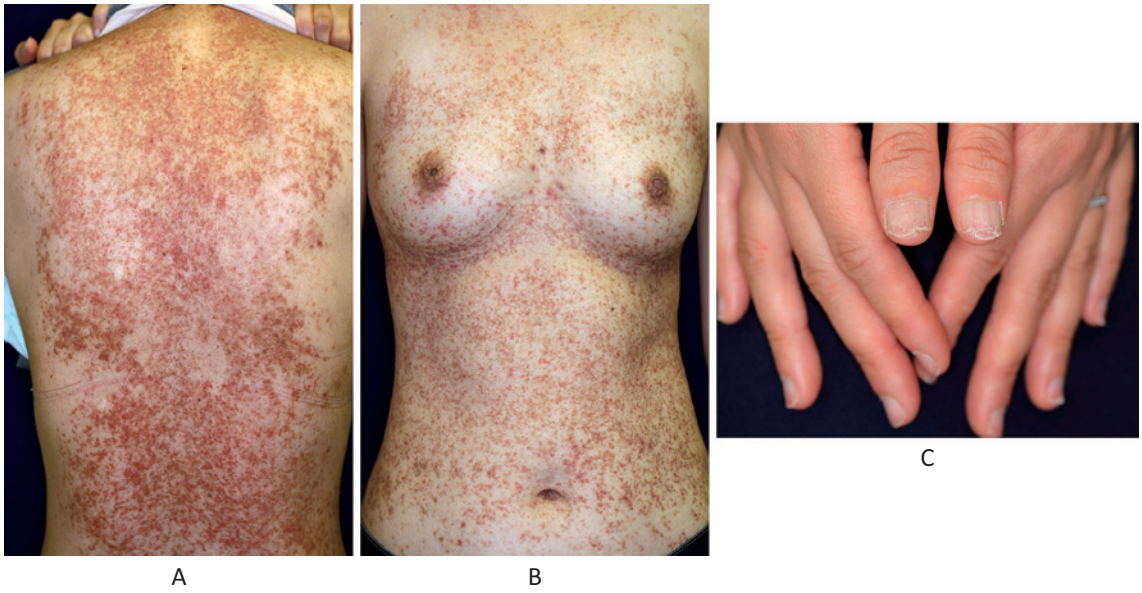

Fig. 1 (A) Multiple slightly crusted brownish-red keratotic papules scattered and coalesced to form verrucous plaques on the back, (B) chest and abdomen. (C) V-shaped notches on the distal end of the nail plate.

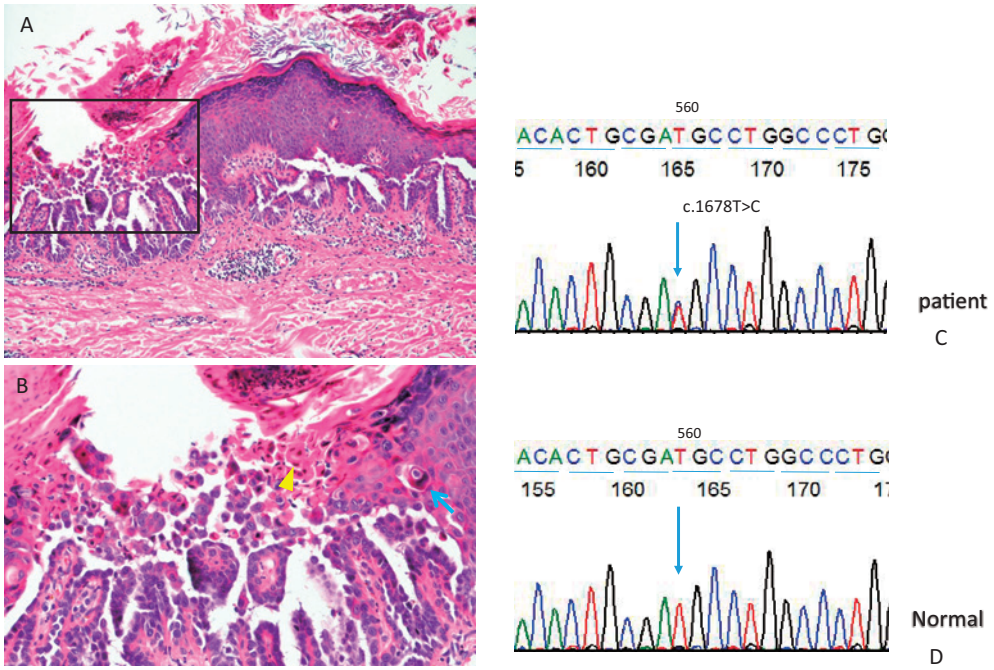

Fig. 2 (A) Histological findings showed focal hyperkeratosis, parakeratosis in the epidermis and suprabasal acantholytic cleft formation. (B) Dyskeratosis with corps ronds (**arrow**) and grains (**arrowhead**). (haematoxylin-eosin, original magnification A×100, B×200). (C) Sequence analysis of the *ATP2A2* gene revealed a nucleotide transition of T to C (1678T>C) in one allele of exon 13, resulting in the amino acid change from cysteine to arginine (C560R) indicated by the arrow. (D) Wild-type sequence of exon 13.

change from cysteine to arginine (p. C560R) (**Fig. 2C and D**).

DD generally responds well to oral retinoids, however we did not choose this treatment due to its teratogenic side effects. Treatment with an oral antihistamine, minocycline (200 mg/day), topical corticosteroids, active vitamin D3 ointment and heparinoid emollients relieved her symptoms over several months with mild residual hyperpigmentation. During one year and a half following up, her symptoms relapsed two times due to catching a cold and stopping treatment by herself.

The same mutation was also detected in her affected

Table 1 *ATP2A2* mutations and clinical features of Japanese patients with DD reported previously

Case number	Patient age, sex (onset age, y)	Family history	Location, Mutation	Amino acid change	Consequence	Protein domain	Clinical Severity[6] Features	Reference (year of publish)
1–4	65F (10y)	–	Exon 14, c.1839C>A	C613X	nonsense		moderate	10 (2001)
	70F (20y)	+	Exon 8, c.961C>T	L321F	missense	Stalk 4	severe	
	65M (30y)	–	Exon 8, c.820A>G	I274V	missense	M3	mild	
	76M (50y)	–	Exon 15, c.2157 G>A	M719I	missense	Hinge domain	moderate	
5–8	ND	–	Exon 7, c.547C>A	E183K	missense	B-strand	ND	11 (2003)
		–	Exon 14, c.2039C>T	P680 L	missense	Hinge domain		
		–	Exon 7, c.548A>T	E183V	missense	B-strand		
		–	Exon 7, Ctgt → ctCATgt	553insCAT	185insH	B-strand		
9–15	77M (30y)/50M (10y)	+	Exon 8, c.697 G>C	G233R	missense	B-strand	mild/severe	12 (2004)
	17F (4y)/13F (12y)	+	Exon 8, c.952T>C	C318R	missense	Stalk 4	severe/mild	
	54F/33F/28F (all 10y)	+	Exon 16, c.2512 G>C	A838P	missense	M7	severe	
	40M	–	Exon 1, c.1A>G	M1V	missense	Start codon	severe	
	13F (11y)	–	Exon 1, c.115A>G	N39D	missense	Upstream stalk	moderate	
	33F (31y)	–	Exon 6, c.539T>G	L180R	missense	B-strand	moderate	
	48M (44y)	–	Exon 15, TGC → TGGC	2170insG	frameshift insertion	Hinge domain	moderate	
16	34F (13y)	+	Exon 15, c.2300A>G	N767S	missense	M5	haemorrhagic variant	13 (2007)
17	20M (11y)	–	Exon 17, c.2541delC		deletion	M7	moderate	14 (2009)
18	22M (10y)	–	Exon 2, c.120_122delGTT	p.Leu41del	deletion	Stalk 1	comedonal type	15 (2010)
19	48M (20y)	+	Exon 15, c.2224 G>A	G742R	missense	Stalk 5	moderate	16 (2012)
20	80M (75y)	–	Exon 14, c.2092 G>C	A698P	missense	ATP-binding domain	mild	8 (2013)
21	67M (47y)	–	Exon 8, c.1043T>C	I348T	missense	Phosphorylation	severe	17 (2013)
22	38F (33y)	–	Intron 10, c.1287+1 G>T	–	splice site	Phosphorylation	moderate	18 (2014)
23	40F	–	Exon 18, c.2721A>C	E907D	missense	M8	moderate	19 (2015)
24	46F (20y)	–	Intron 1, c.119-2A>T	–	splice site	Stalk 1	moderate	20 (2015)
25	41F	+	Intron 10, c.1288-6A>G	–	splice site	Phosphorylation	ND (bipolar disorder)	4 (2016)
26	66M (65y)	–	Exon 8, c.953 G>A	C318T	missense	Stalk 4	moderate (schizophrenia)	21 (2016)
This study	34F (24y)	+	Exon 13, c.1678T>C	C560R	missense	ATP-binding domain	moderate	

M, transmembrane domain; ND, no data

father who showed mild phenotype, which pathologically confirmed the diagnosis of DD combined with lichen amyloidosis (data not shown).

Discussion

More than 248 *ATP2A2* mutations have now been reported in DD patients[4]. The mutations, including missense, nonsense, frame-shift or inframe insertion/deletion and splice-site mutations are spread throughout the *ATP2A2* gene without hot spots and most are family-specific[3,5,6]. Ringpfeil et al.[6] noted that 15 of 92 mutations have been reported more than once, in which 12 were identified in two unrelated individuals/families. No consistent genotype-phenotype correlations have been established[3,6]. There are considerable inter/intrafamilial variations in DD, which suggests that additional modifying genes and/or environmental factors influence the phenotype[3,6]. *ATP2A2* mutations cause the dominant DD phenotype through haploinsufficiency[2].

The mutation C560R, located in the ATP-binding domain, decreases the protein expression of SERCA2[4]. The change from a hydrophobic amino acid into a basic one, a non-conservative amino acid change, alters the charge, polarity, hydrophobicity and size of the amino acid residue, and likely interferes with SERCA2 function[3].

Jacobsen et al.[7] reported the same mutation in a sporadic DD with schizoid personality psychosis and a pedigree with bipolar disorder and they suggested that mutations in the ATP-binding domain might have relevance in mood disorders. But in our case and another mild phenotype Japanese DD case[8] with mutation in the ATP-binding domain (A698P), no neuropsychiatric symptoms were found. Three pedigrees with nonsense or frameshift insertion/deletion mutations in the ATP-binding domain, were mild/moderate, and two of them had neuropsychiatric symptoms[3]. Neuropsychiatric abnormalities did not seem to be associated with the types of *ATP2A2* mutations[9]. The association between DD and neuropsychiatric abnormalities may be a pleiotropic effect of *ATP2A2* mutations on both the skin and brain[4,7].

In Japan, 26 mutations in the *ATP2A2* gene in 7 pedigrees and 19 sporadic cases with DD have been reported[4,8,10–21]. The genetic and clinical features of Japanese DD patients are summarized in **Table 1**. There were no hot spot mutations and most mutations were of the missense type (18 of 26 mutations, 69%). P680L, C318R, A838P, M1V, N39D, N767S, I348T have been reported previously. C318R, occurring in stalk 4, exhibited a severe erosive phenotype[3]. C318R and G233R[12], A838P and M1V[9] had phenotypic variations within families. N39D and I348T were identified in moderate DD with depression or behavioral problems[6]. Mutations with severe phenotype affected the cytoplasmic stalk, transduction, phosphorylation and transmembrane domains M6/M7[6]. N767S, the most frequently reported mutation in DD, has been reported 11 times[5]. This mutation was associated with an acral haemorrhagic variant of DD or neuropsychiatric abnormalities in some cases, but without these features in others[5], and the acral haemorrhagic variant of DD might also be caused by mutation C268F in M3[9]. Wada et al.[22] reported a case of segmental DD with I54V found only in the affected skin, but not in the peripheral leucocytes, which represented genetic mosaicism resulting from postzygotic mutations in the *ATP2A2* gene. In these reported Japanese DD cases, one pedigree and one sporadic case had neuropsychiatric symptoms. In summary, our review of Japanese DD with mutations confirms that most mutations were of the missense type; no consistent genotype-phenotype correlations were found.

Conflict of Interest: The authors declare no conflict of interest.

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