RESULTS

Demographic data for the 67 448 patients

Among the 67 448 patients, 32 062 (47.54%) cases were recruited from university hospitals, 12 709 (18.84%) from district-based hospital and 22 677 (33.62%) from private clinics (Table 1). More patients were enrolled in August 2007 (18 103) than in February 2008 (15 467) (Table 1). With regards to the age distribution, the group aged 71–75 years (6157; 9.13%) was the biggest, followed by groups aged 66–70 (5629; 8.35%), 56–60 (5543; 8.22%) and 61–65 (5413; 8.03%) (Table 2). For patients aged under 20 years, the group aged 0–5 years formed the biggest population (4192; 6.22%). Among the 67 448 patients, there were 30 899 (46.1%) males and 36 125 (53.9%) females; the sex of 424 patients was not described. Female patients aged between 16 and 60 years tended to visit dermatology clinics more frequently than their male counterparts (Table 2).

Prevalence of skin disorders

We classified skin diseases into 85 categories, as listed in Table 3, and determined the prevalence of each. The 20 most common diseases were miscellaneous eczema (12 590; 18.67%) followed, in order, by atopic dermatitis (6733; 9.98%), tinea pedis (4379; 6.49%), urticaria/angioedema (3369; 4.99%), tinea unguium (3231; 4.79%), viral warts (3028; 4.49%), psoriasis (2985; 4.43%), contact dermatitis (2643, 3.92%), acne (2430; 3.6%), seborrheic dermatitis (2213; 3.28%), hand eczema (2024; 3%), miscellaneous benign skin tumors (1666; 2.47%), alopecia areata (1653; 2.45%), herpes zoster/zoster-associated

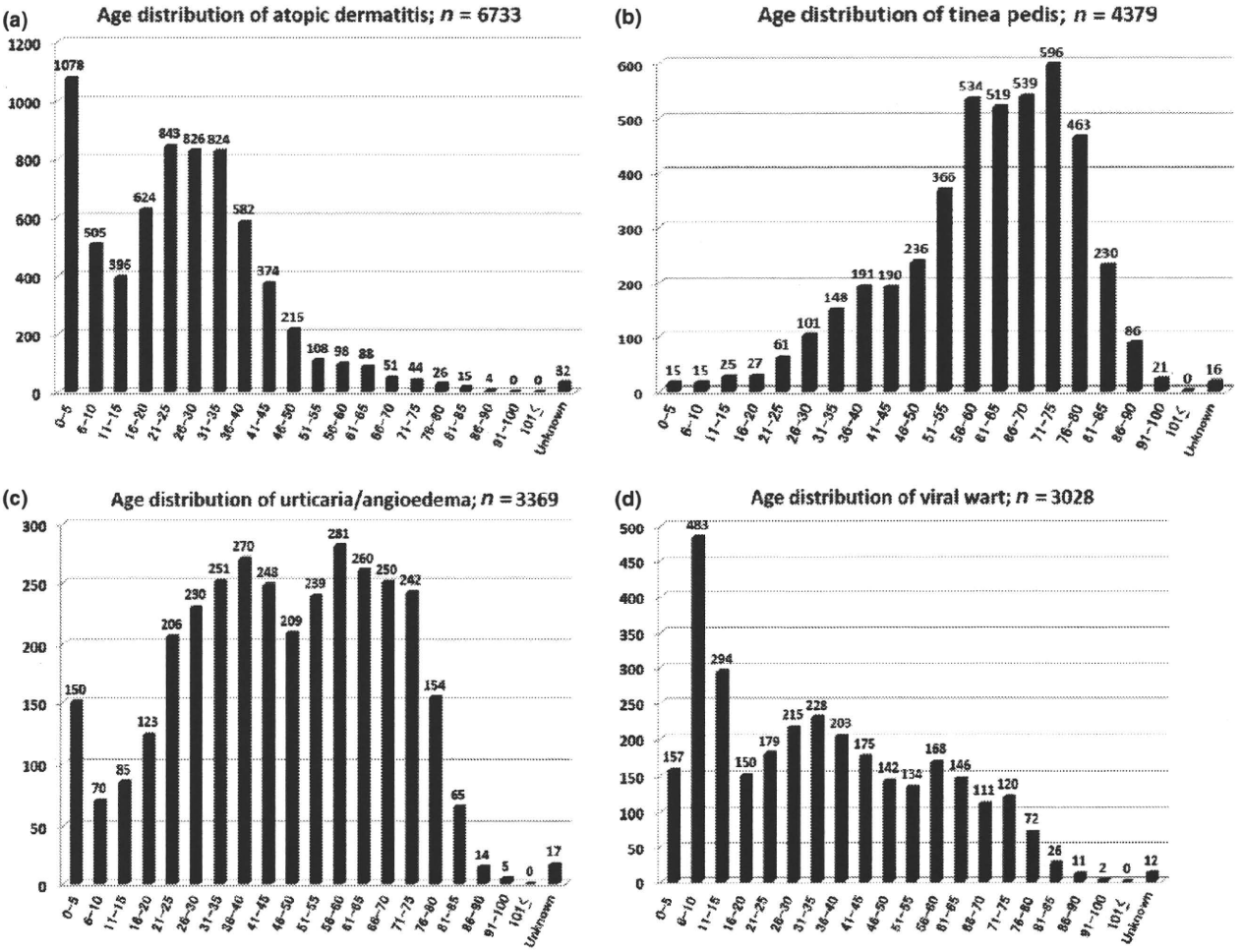


Figure 1. Age distribution of atopic dermatitis, tinea pedis, urticaria/angioedema and viral wart.

pain (1609; 2.39%), skin ulcers (non-diabetic) (1334; 1.98%), prurigo (1229; 1.82%), epidermal cysts (1194; 1.77%), vitiligo vulgaris (1134; 1.68%), seborrheic keratosis (1095; 1.62%) and drug eruption/toxicoderma (1018; 1.51%). These top 20 categories covered 57 577 (85.34%) of the 67 448 patients (Table 3).

Age distributions of common diseases

The age distribution of atopic dermatitis was biphasic, peaking at 0–5 and 21–35 years of age (Fig. 1a). Tinea pedis peaked at 56–75 years of age (Fig. 1b). Tinea unguium showed a similar pattern (data not shown). Urticaria/angioedema showed a triphasic distribution pattern (Fig. 1c), whereas viral warts peaked at 6–15 years of age (Fig. 1d). Psoriasis peaked at 56–65 years of age (Fig. 2a). The age distribution for contact dermatitis was somewhat evenly dispersed (Fig. 2b). The peak age for acne was 16–25 years (Fig. 2c), whereas that for seborrheic dermatitis was 71–75 (Fig. 2d). Hand eczema was distributed evenly in adults (Fig. 3a). The peak age for alopecia areata was 31–35 years (Fig. 3b). Herpes zoster/zoster-associated pain and prurigo were prominent in elderly patients (Fig. 3c,d). Epidermal cysts occurred in adults of all ages (Fig. 4a). Vitiligo vulgaris and drug eruption/toxicoderma were preponderant in elderly people (Fig. 4b,c). Notably, the age distribution for burns peaked in the group aged 0–5 years (Fig. 4d).

In Tables 4 and 5, we list the top five skin disorders for each age group. Miscellaneous eczema appeared in every age group, whereas atopic dermatitis was among the top five diseases for age groups under 50 years. The disease encountered most frequently in groups aged 6–40 years was atopic dermatitis.

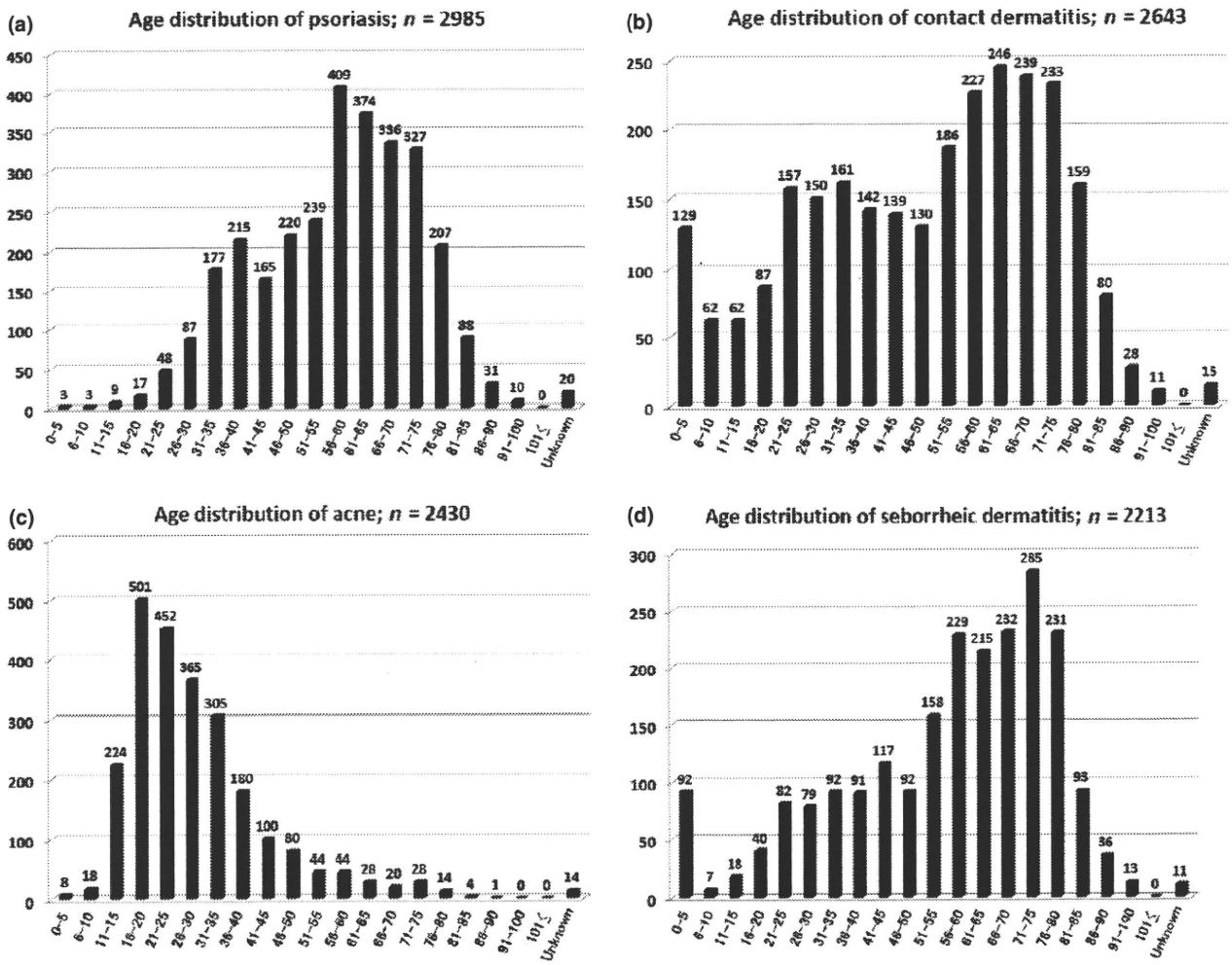


Figure 2. Age distribution of psoriasis, contact dermatitis, acne and seborrheic dermatitis.

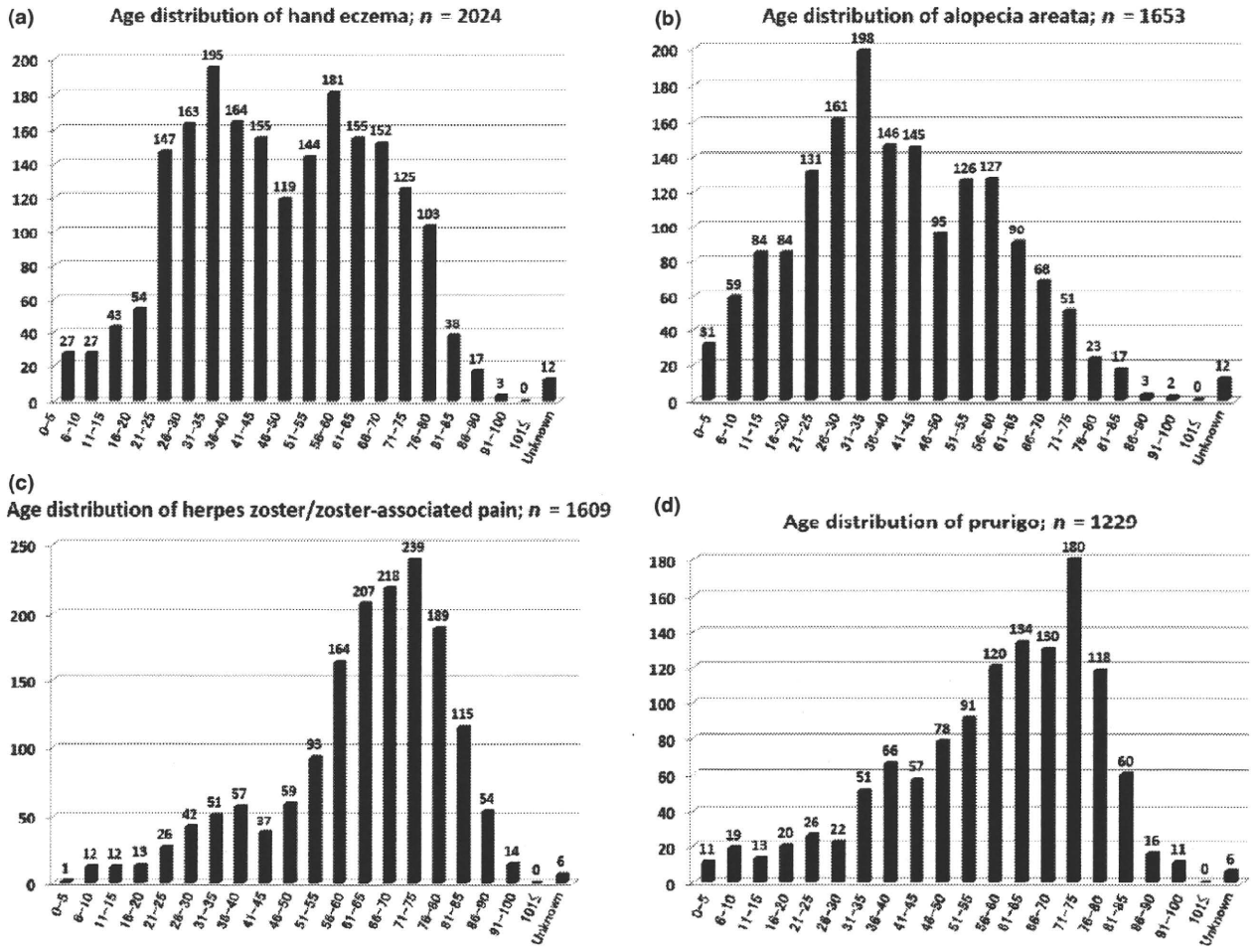


Figure 3. Age distribution of hand eczema, alopecia areata, herpes zoster/zoster-associated pain and prurigo.

Molluscum and impetigo were common in patients aged 0–10 years. Viral warts were among the top five diseases for groups aged 6–45 years. Acne was common in groups aged 11–35 years. Urticaria/angioedema was among the top five diseases for a wide range of age groups from 11–70 years old. Tinea pedis was common in groups aged above 41 years old. Psoriasis appeared in the top five diseases in middle-aged and older people with ages ranging 46–80 years old.

Sex differences

Difference in the incidence of skin disorders between the sexes are shown in Table 6. The prevalence of diabetic dermatoses, psoriasis, androgenic alopecia, syphilis and erythroderma in males was more than twice that in females, whereas the prevalence of hand eczema, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, reticular/racemous livedo, pigmented nevus, chloasma/senile freckle, erythema nodosum and rosacea/rosacea-like dermatitis was more than twice as high in females than males (Table 6).

Correlation between patient numbers and the average low temperature, average high temperature and average humidity in the months of clinic visits

Because this study was a nationwide survey for Japan, a wide variation of climates had to be considered. We therefore searched for correlations between patient numbers and average low temperature, average high temperature and average humidity of the month in which patients visited clinics. The numbers of visiting patients diagnosed with urticaria/angioedema (Fig. 5), insect bites (Fig. 5), tinea pedis (Fig. 6)

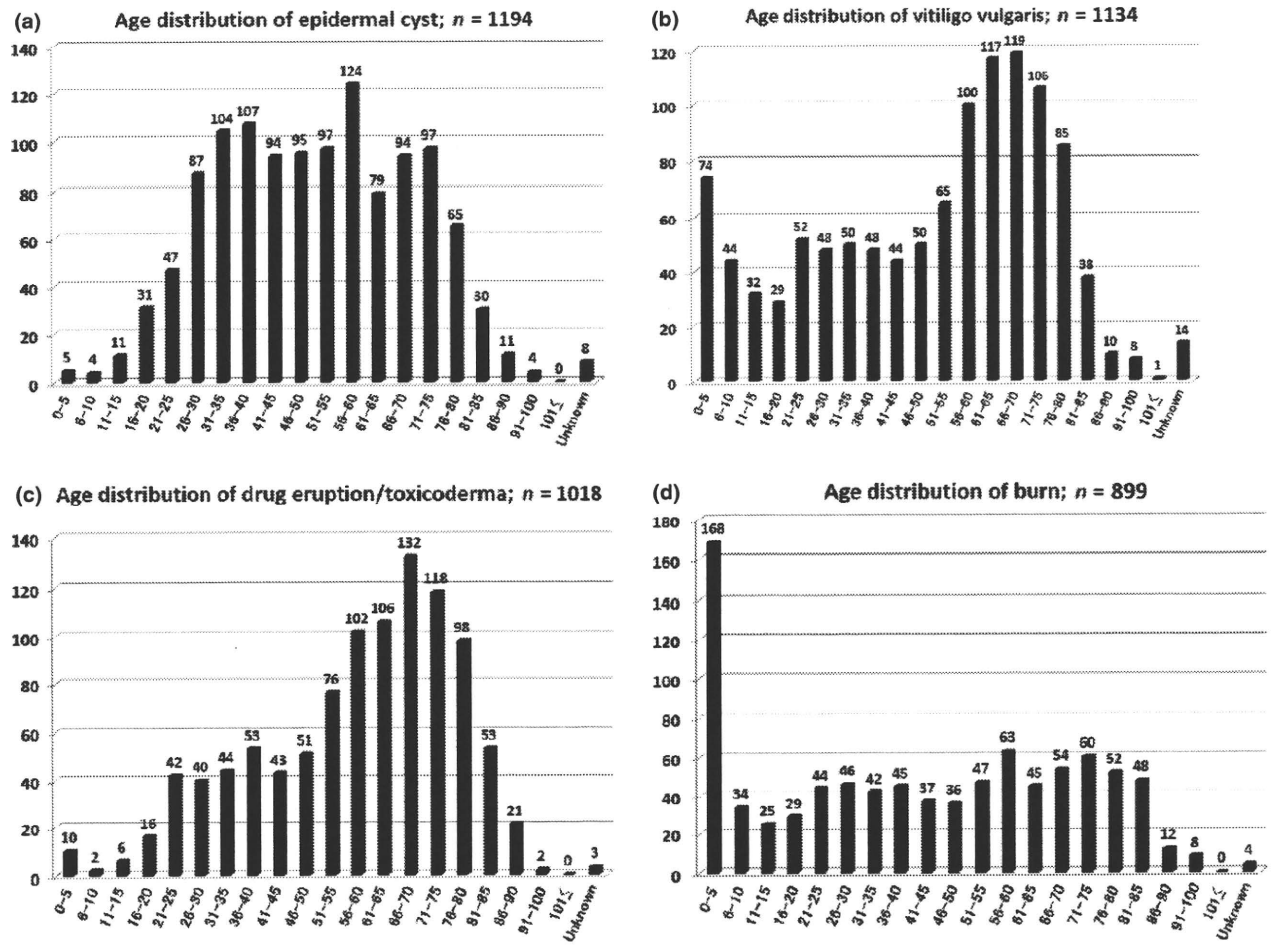


Figure 4. Age distribution of epidermal cyst, vitiligo vulgaris, drug eruption/toxicoderma and burn.

or impetigo (Fig. 6) showed a significant correlation with the average low temperature and with the average high temperature (data not shown). The numbers of visiting patients diagnosed with atopic dermatitis, contact dermatitis or molluscum contagiosum were also positively correlated with the average low temperature and average high temperature (data not shown). The numbers of patients diagnosed with seborrheic dermatitis showed a negative correlation with the average humidity (Fig. 7). The average humidity was also significantly and negatively correlated with atopic dermatitis, hand eczema and prurigo (data not shown).

DISCUSSION

There are a number of limitations and biases in hospital-based prevalence studies, including institutional specificity (university hospital, pivotal local hospital or private clinic), differences in localization, climatic and seasonal differences, and differences in skills in diagnosis.[1,4–6] This study, conducted in fiscal year 2007 by the Japanese Dermatological Association, recruited 76 university hospitals, 55 district-based pivotal hospitals and 59 private clinics (190 clinics in total). We analyzed data for 67 448 patients that were collected seasonally from 170 clinics. This nationwide study is first of its kind in Japan, and its nature appears to eliminate, at least in part, some of the above-mentioned biases of hospital-based prevalence study.

In fiscal year 2007, eczematous and fungal diseases were commonly reported in dermatological clinics in Japan. The 20 most common categories of skin disorder were diagnosed in more than 85% of patients presenting dermatological complaints. A

Table 4. Top five skin disorders in each age group

0–5 years old (*n* = 4192)	
Miscellaneous eczema	1229; 29.32%
Atopic dermatitis	1078; 25.72%
Molluscum contagiosum	425; 10.14%
Impetigo contagiosum	291; 6.94%
Miscellaneous benign skin tumors	226; 5.39%
6–10 years old (*n* = 2099)	
Atopic dermatits	505; 24.06%
Viral wart	483; 23.01%
Miscellaneous eczema	355; 16.91%
Molluscum contagiosum	144; 6.86%
Impetigo contagiosum	110; 5.24%
11–15 years old (*n* = 1711)	
Atopic dermatits	396; 23.14%
Viral wart	294; 17.18%
Acne	224; 13.09%
Miscellaneous eczema	214; 12.51%
Urticaria/angioedema	85; 4.97%
16–20 years old (*n* = 2270)	
Atopic dermatits	624; 27.49%
Acne	501; 22.07%
Miscellaneous eczema	269; 11.85%
Viral wart	150; 6.61%
Urticaria/angioedema	123; 5.42%
21–25 years old (*n* = 3219)	
Atopic dermatits	843; 26.19%
Acne	452; 14.04%
Miscellaneous eczema	407; 12.64%
Urticaria/angioedema	206; 6.4%
Viral wart	179; 5.56%
26–30 years old (*n* = 3516)	
Atopic dermatits	826; 23.49%
Miscellaneous eczema	451; 12.83%
Acne	365; 10.38%
Urticaria/angioedema	230; 6.54%
Viral wart	215; 6.11%
31–35 years old (*n* = 4050)	
Atopic dermatits	824; 20.35%
Miscellaneous eczema	551; 13.6%
Acne	305; 7.53%
Urticaria/angioedema	251; 6.2%
Viral wart	228; 5.63%
36–40 years old (*n* = 3807)	
Atopic dermatits	582; 15.29%
Miscellaneous eczema	503; 13.21%
Urticaria/angioedema	270; 7.09%
Psoriasis	215; 5.65%
Viral wart	203; 5.33%
41–45 years old (*n* = 3298)	
Miscellaneous eczema	454; 13.77%
Atopic dermatits	374; 11.34%
Urticaria/angioedema	248; 7.52%
Tinea pedis	190; 5.76%
Viral wart	175; 5.31%
46–50 years old (*n* = 3201)	
Miscellaneous eczema	453; 14.15%
Tinea pedis	236; 7.37%
Psoriasis	220; 6.87%
Atopic dermatits	215; 6.72%
Urticaria/angioedema	209; 6.53%

Table 5. Top five skin disorders in each age group

51–55 years old (*n* = 4062)	
Miscellaneous eczema	676; 16.64%
Tinea pedis	366; 9.01%
Psoriasis	239; 5.88%
Urticaria/angioedema	239; 5.88%
Tinea unguium	226; 5.56%
56–60 years old (*n* = 5540)	
Miscellaneous eczema	910; 16.43%
Tinea pedis	534; 9.64%
Psoriasis	409; 7.38%
Tinea unguium	331; 5.97%
Urticaria/angioedema	281; 5.07%
61–65 years old (*n* = 5415)	
Miscellaneous eczema	1016; 18.76%
Tinea pedis	519; 9.58%
Tinea unguium	393; 7.26%
Psoriasis	374; 6.91%
Urticaria/angioedema	260; 4.8%
66–70 years old (*n* = 5628)	
Miscellaneous eczema	1141; 20.27%
Tinea pedis	539; 9.58%
Tinea unguium	463; 8.23%
Psoriasis	336; 5.97%
Urticaria/angioedema	250; 4.44%
71–75 years old (*n* = 6157)	
Miscellaneous eczema	1457; 23.66%
Tinea pedis	596; 9.68%
Tinea unguium	566; 9.19%
Psoriasis	327; 5.31%
Seborrheic dermatitis	285; 4.63%
76–80 years old (*n* = 4778)	
Miscellaneous eczema	1304; 27.29%
Tinea pedis	463; 9.69%
Tinea unguium	401; 8.39%
Seborrheic dermatitis	231; 4.83%
Psoriasis	207; 4.33%
81–85 years old (*n* = 2636)	
Miscellaneous eczema	725; 27.5%
Tinea unguium	233; 8.84%
Tinea pedis	230; 8.73%
Herpes zoster/zoster-associated pain	115; 4.36%
Seborrheic dermatitis	93; 3.53%
86–90 years old (*n* = 1099)	
Miscellaneous eczema	307; 27.93%
Tinea unguium	86; 7.83%
Tinea pedis	79; 7.19%
Pressure ulcer	65; 5.91%
Skin ulcer (nondiabetic)	63; 5.73%
91–100 years old (*n* = 427)	
Miscellaneous eczema	110; 25.76%
Pressure ulcer	43; 10.07%
Squamous cell carcinoma/Bowen's disease	35; 8.2%
Skin ulcer (non-diabetic)	28; 6.56%
Bullous pemphigoid	22; 5.15%

Table 6. Sex differences in skin diseases

	Total; Male; Female		Total; Male; Female
Burn	892, 1.33%; 414, 1.34%; 478, 1.32%	Miscellaneous viral disorders	349, 0.52%; 171, 0.55%; 178, 0.49%
Trauma	406, 0.61%; 196, 0.63%; 210, 0.58%	Syphilis	24, 0.04%; 16, 0.05%; 8, 0.02%
Skin ulcer (nondiabetic)	1318, 1.97%; 605, 1.96%; 713; 1.97%	Miscellaneous sexually transmitted diseases	40, 0.06%; 26, 0.08%, 14, 0.04%
Pressure ulcer	606, 0.9%; 313, 1.01%; 293, 0.81%	Bullous pemphigid	509, 0.76%; 208, 0.67%; 301, 0.83%
Miscellaneous physico-chemical skin damage	675, 1.01%; 303, 0.98%; 372, 1.03%	Pemphigus	416, 0.62%; 180, 0.58%; 236, 0.65%
Diabetic dermatoses	432, 0.64%; 300, 0.97%; 132, 0.37%	Miscellaneous bullous diseases	139, 0.21%; 67, 0.22%; 72, 0.2%
Atopic dermatitis	6707, 10.01%; 3486, 11.28%; 3221, 8.92%	Systemic sclerosis	609, 0.91%; 94, 0.3%; 515, 1.43%
Hand eczema	2009, 3%; 532, 1.72%; 1477, 4.09%	Systemic lupus erythematosus	520, 0.78%; 72, 0.23%; 448, 1.24%
Contact dermatitis	2629, 3.92%; 902, 2.92%; 1727, 4.78%	Dermatomyositis	300, 0.45%; 76, 0.25%; 224, 0.62%
Seborrheic dermatitis	2201, 3.28%; 1295, 4.19%; 906, 2.51%	Miscellaneous collagen diseases	911, 1.36%; 209, 0.68%; 702, 1.94%
Miscellaneous eczema	12523, 18.68%; 6289, 20.35%, 6234, 17.26%	Anaphylactoid purpura	169, 0.25%; 72, 0.23%; 97, 0.27%
Urticaria/angioedema	3355, 5.01%; 1251, 4.05%; 2104, 5.82%	Reticular/racemous livedo	80, 0.12%; 21, 0.07%; 59, 0.16%
Prurigo	1216, 1.81%; 755, 2.44%; 461, 1.28%	Miscellaneous vasculitis/purpura/ circulatory disturbance	625, 0.93%; 239, 0.77%; 386, 1.07%
Drug eruption/toxicoderma	1012, 1.51%; 436, 1.41%; 576, 1.59%	Mycosis fungoides	418, 0.62%; 244, 0.79%; 174, 0.48%
Psoriasis	2967, 4.43%; 2138, 6.92%; 829, 2.29%	Miscellaneous lymphomas	283, 0.42%; 149, 0.48%; 134, 0.37%
Palmoplantar pustulosis	828, 1.24%; 284, 0.92%; 544, 1.51%	Pigmented nevus	703, 1.05%; 206, 0.67%; 497, 1.38%
Miscellaneous pustulosis	170, 0.255%; 67, 0.22%; 103, 0.29%	Seborrheic keratosis	1090, 1.63%; 537, 1.74%; 553, 1.53%
Lichen planus	200, 0.3%; 80, 0.26%; 120, 0.33%	Soft fibroma/achrochordon	228, 0.34%; 78, 0.25%; 150, 0.42%
Miscellaneous inflammatory keratotic disorders	241, 0.36%; 95, 0.31%; 146, 0.4%	Epidermal cyst	1183, 1.77%; 713, 2.31%; 470, 1.3%
Tylosis/clavus	911, 1.36%; 292, 0.95%; 619, 1.71%	Lipoma	171, 0.26%; 92, 0.3%; 79, 0.22%
Ichthyosis	61, 0.09%, 31, 0.1%; 30, 0.08%	Dermatofibroma	110, 0.16%; 44, 0.14%, 66, 0.18%
Miscellaneous keratinization disorders	502, 0.75%; 192, 0.62%; 310, 0.86%	Miscellaneous benign skin tumors	1651, 2.46%; 673, 2.18%; 978, 2.71%
Ingrown nail	594, 0.89%; 197, 0.64%; 397, 1.1%	Actinic keratosis	256, 0.38%; 129, 0.42%; 127, 0.35%
Miscellaneous nail disorder	396, 0.59%; 123, 0.4%; 273, 0.76%	Basal cell carcinoma	324, 0.48%; 166, 0.54%; 158, 0.44%
Alopecia areata	1644, 2.45%; 557, 1.8%; 1087, 3.01%	Squamous cell carcinoma/Bowen's disease	447, 0.67%; 272, 0.88%; 175, 0.48%
Androgenic alopecia	208, 0.31%; 198, 0.64%; 10, 0.03%	Paget's disease	221, 0.33%; 136, 0.44%; 85, 0.24%
Miscellaneous skin appendage disorders	266, 0.4%, 77, 0.25%; 189, 0.52%	Malignant melanoma	802, 1.2%; 395, 1.28%; 407, 1.13%
Scabies	96, 0.14%; 50, 0.16%; 46, 0.13%	Miscellaneous malignant skin tumors	531, 0.79%; 291, 0.94%; 240, 0.66%
Insect bite	762, 1.14%; 285, 0.92%; 477, 1.32%	Vitiligo vulgaris	1123, 1.68%; 473, 1.53%; 650, 1.8%
Tinea pedis	4363, 6.51%; 2225, 7.2%; 2138, 5.92%	Chloasma/senile freckle	334, 0.5%; 18, 0.06%; 316, 0.87%
Tinea unguium	3216, 4.8%; 1581, 5.12%; 1635, 4.53%	Miscellaneous pigmented disorders	154, 0.23%; 30, 0.1%; 124, 0.34%
Miscellaneous tinea	607, 0.91%; 404, 1.31%; 203, 0.56%	Erythema multiforme	194, 0.29%; 89, 0.29%; 105, 0.29%
Candidiasis	406, 0.61%; 176, 0.57%; 230, 0.64%	Erythema nodosum	111, 0.17%; 12, 0.04%; 99, 0.27%
Miscellaneous mycosis	209, 0.31%; 117, 0.38%; 92, 0.25%	Miscellaneous disorders with erythematous plaques	130, 0.19%; 40, 0.13%; 90, 0.25%
Acne	2423, 3.62%; 757, 2.45%; 1666, 4.61%	Nevus/phacomatosis (other than pigmented nevus)	266, 0.4%; 89, 0.29%; 177, 0.49%
Impetigo contagiosum	505, 0.75%; 283, 0.92%; 222, 0.61%	Rosacea/rosacea-like dermatitis	148, 0.22%; 36, 0.12%; 112, 0.31%
Folliculitis	749, 1.12%; 432, 1.4%; 317, 0.88%	Granulomatous diseases	192, 0.29%; 65, 0.21%; 127, 0.35%
Erysipelas	81, 0.12%; 35, 0.11%; 46, 0.13%	Keloid/hypertrophic scar	184, 0.27%; 73, 0.24%; 111, 0.31%
Cellulitis	589, 0.88%; 304, 0.98%; 285, 0.79%	Cheilitis/angular cheilitis/mucous membrane diseases	94, 0.14%; 38, 0.12%; 56, 0.16%
Miscellaneous bacterial infection	909, 1.36%; 497, 1.61%; 412, 1.14%	Erythroderma	62, 0.09%; 44, 0.14%; 18, 0.05%
Molluscum contagiosum	602, 0.9%; 327, 1.06%; 275, 0.76%	Other diseases	662, 0.99%; 315, 1.02%; 347, 0.96%
Herpes simplex	688, 1.03%; 266, 0.86%; 422, 1.17%	Total	67 024, 100%; 30 899, 100%; 36 125, 100%
Herpes zoster/zoster-associated pain	1599, 2.39%; 694, 2.25%; 905, 2.51%		
Viral wart	3016, 4.5%; 1388, 4.49%; 1628, 4.51%		

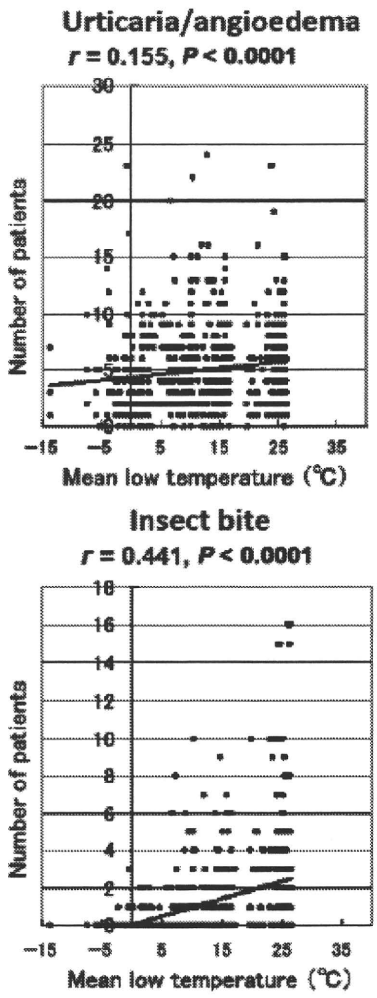


Figure 5. Correlation between patient numbers and mean low temperature in urticaria/angioedema and insect bite.

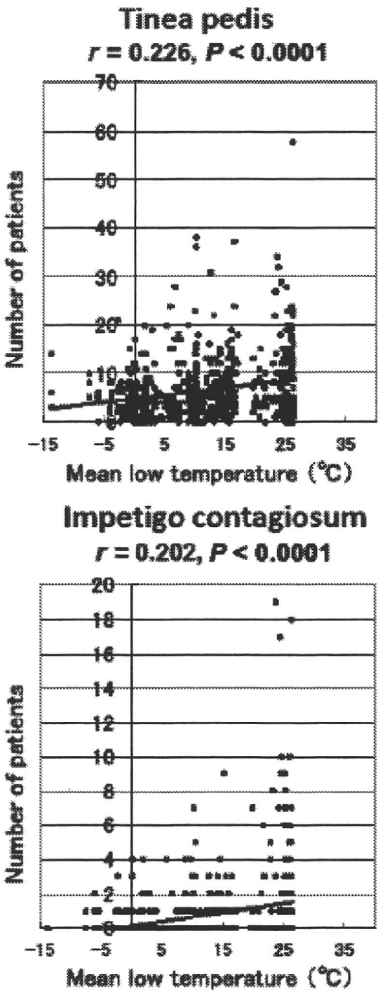


Figure 6. Correlation between patient numbers and mean low temperature in tinea pedis and impetigo contagiosum.

previous hospital-based study in Turkey[3] reported that the five most common disorders were atopic dermatitis, diaper dermatitis, impetigo, seborrheic dermatitis and miliaria in children aged 0–2 years; atopic dermatitis, impetigo, warts, contact dermatitis and insect bites in children aged 3–5 years; contact dermatitis, warts, atopic dermatitis, pruritus and impetigo in children aged 6–11 years; and acne, contact dermatitis, warts, seborrheic dermatitis and pruritus in children aged 12–16 years. For Dutch children aged 0–17 years old in 2001, the incidence rates per person-year of skin disorders were, in descending order, warts 34.3, dermatophytosis 25.4, contact dermatitis/other eczema 22.9, impetigo 20.5, laceration/cuts 20.3, atopic

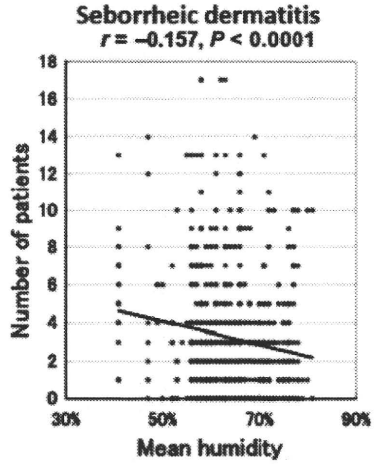


Figure 7. Negative correlation between patient numbers and mean humidity in seborrheic dermatitis.

dermatitis 16.5, moniliasis/candidasis 9.8 and molluscum contagiosum 9.5.[2] Although the order of each disease differed from country to country, atopic dermatitis, miscellaneous eczematous diseases, impetigo and warts appear to share their top rankings in pediatric dermatology, and this was also the case in Japan. Similar observations were also made in 1105 pediatric outpatients aged 0–15 years who visited the hospital of Aarau in Switzerland between 1998 and 2001.[7]

In Turkey, Yalçin *et al.*[8] examined records for 4099 geriatric patients over 65 years old who were admitted to the Ankara Numune Educational and Research Hospital from 1999 through 2003. The five most frequently diagnosed diseases were as follows: in the group aged 65–74 years, eczematous dermatitis, fungal infections, pruritus and bacterial and viral infections; in the group aged 75–84 years, eczematous dermatitis, pruritus, and fungal, viral and bacterial infections; and in the group aged over 85 years, pruritus, eczematous dermatitis, precancerous lesions and skin carcinomas, and viral and fungal infections.[8] In the present study, the Japanese geriatric population was also found to suffer very frequently from miscellaneous eczema and tinea pedis/unguium. In addition, there was a high incidence of psoriasis in elderly Japanese patients. As expected, we found conspicuous differences in the incidence of collagen diseases between the two sexes. A preponderance of collagen diseases in females was also evident in Yalçin's study.[8]

It should be emphasized again that this study was simply a measure of skin disorders in patients attending ordinary dermatology clinics in Japan. The study holds various limitations and biases, but it appears to highlight the current situation regarding patients presenting dermatological problems in Japan.

ACKNOWLEDGMENTS

We sincerely appreciate the considerable contribution and devotion of each clinic that participated in this study. The data management and statistical analysis was organized by EBMs Co., Ltd.

REFERENCES

1 Julian CG. Dermatology in general practice. *Br J Dermatol* 1999; **141**: 518–520.
2 Mohammedamin RS, van der Wouden JC, Koning S *et al.* Increasing incidence of skin disorders in children? A comparison between 1987 and 2001 *BMC Dermatol* 2006; **6**: 4.
3 Tamer E, Ilhan MN, Polat M, Lenk N, Alli N. Prevalence of skin diseases among pediatric patients in Turkey. *J Dermatol* 2008; **35**: 413–418.
4 Steer AC, Jenney AW, Kado J *et al.* High burden of impetigo and scabies in a tropical country. *PLoS Negl Trop Dis* 2009; **3**: e467.
5 Elliot AJ, Cross KW, Smith GE, Burgess IF, Fleming DM. The association between impetigo, insect bites and air temperature: a retrospective 5-year study (1999–2003) using morbidity data collected from a sentinel general practice network database. *Fam Pract* 2006; **23**: 490–496.
6 Rørtveit S, Rortveit G. Impetigo in epidemic and non-epidemic phases: an incidence study over 4 (1/2) years in a general population. *Br J Dermatol* 2007; **157**: 100–105.
7 Wenk C, Itin PH. Epidemiology of pediatric dermatology and allergology in the region of Aargau, Switzerland. *Pediatr Dermatol* 2003; **20**: 482–487.
8 Yalçin B, Tamer E, Toy GG, Oztaş P, Hayran M, Alli N. The prevalence of skin diseases in the elderly: analysis of 4099 geriatric patients. *Int J Dermatol* 2006; **45**: 672–676.

[2] Gudbjartsson DF, Thorvaldsson T, Kong A, Gunnarsson G, Ingolfsdottir A. Allegro version 2. Nat Genet 2005;37:1015–6.
[3] Matise TC, Chen F, Chen W, De La Vega FM, Hansen M, He C, et al. A second-generation combined linkage physical map of the human genome. Genome Res 2007;17:1783–6.

Musharraf Jelani
Muhammad Tariq
Department of Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan

Iftikhar Ahmad Jan
Hazrat Ullah
Department of Pediatric Surgery, National Institute of Rehabilitation Medicine (NIRM), Islamabad, Pakistan

Muhammad Naeem
Department of Biotechnology, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan

Wasim Ahmad*
Department of Biochemistry, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan

*Corresponding author. Tel.: +92 51 90643003; fax: +92 51 9205753
E-mail address: ahmad115@hotmail.com
wahmad@qau.edu.pk (W. Ahmad)

30 June 2010
doi:10.1016/j.jdermsci.2010.11.014

Letter to the Editor

New insight into genotype/phenotype correlations in *ABCA12* mutations in harlequin ichthyosis

Harlequin ichthyosis (HI) is a severe and often fatal congenital ichthyosis with an autosomal recessive inheritance pattern [1]. The clinical features include thick, plate-like scales with ectropion, eclabium and flattened ears. *ABCA12* mutations underlie HI [2,3] and it was clarified that HI is caused by severe functional defects in the keratinocyte lipid transporter ABCA12 [2]. To date, various *ABCA12* mutations have been reported in HI patients [4]. However, genotype/phenotype correlations in *ABCA12* mutations have been poorly elucidated. In order to obtain clues to understand genotype/phenotype correlations in *ABCA12* mutations, we report two HI patients from two independent Japanese families, who were compound heterozygotes for *ABCA12* mutations.

Patient 1 is the second child of healthy, unrelated Japanese parents. The skin of the baby girl was covered with white, diamond shaped plaques at birth (Fig. 1a). After therapy with oral retinoids and local application of white petrolatum, in a humid incubator, the scales gradually detached and passive and spontaneous mobility of the joints increased. Now at the age of 1 year and 7 months, her general condition is good, although she still has white to grey scales on a background of erythematous skin over her entire body. Patient 2 is the fourth child of healthy, unrelated Japanese parents. Her older brother had a history of congenital ichthyosis and died in early infancy. The skin of the newborn showed serious symptoms with thick, white, diamond shaped plaques, partly bordered by bleeding fissures (Fig. 1c). Although she had therapy with oral retinoids and local application of white petrolatum, in a humid incubator, her clinical symptoms failed to show any apparent improvement and she died when she was 5 months old.

Skin biopsies showed thick stratum corneum in both patients (Fig. 1d–g). In Patient 2, parakeratosis was observed in the epidermis and a sparse inflammatory cell infiltration was seen in the superficial dermis (Fig. 1e inset). Electron microscopy (Hitachi, Tokyo, Japan) revealed a large number of abnormal, variously sized lipid droplets that accumulated in the cornified cells of both patients' epidermis.

Mutational analysis of *ABCA12* was performed in both patients and their families. Each genomic DNA sample was subjected to PCR amplification, followed by direct automated sequencing. Oligonucleotide primers and PCR conditions used for amplification of all exons 1–53 of *ABCA12* were originally derived from the report by Lefèvre et al. [5] and were partially modified for the present study. The entire coding region including the exon/intron boundaries for both forward and reverse strands from the patients, their parents and 50 healthy Japanese controls were also sequenced. Both patients had the same paternal novel nonsense mutation p.Arg1515X (Fig. 1h) which leads to truncation of the first ATP-binding cassette within ABCA12 likely resulting in ABCA12 loss of function (Fig. 2a). On the other allele, Patient 1 had a maternal recurrent splice acceptor site mutation c.3295-2A>G (Fig. 1h). This splice site mutation was reported in an unrelated Japanese family with HI and was shown to lead to comparable amounts of 2 splice pattern variants [2]. The first mutant transcript would result in a 3 amino acids deletion (1099_1101delYMK). These 3 amino acids are located in the first transmembrane domain and are highly conserved (Fig. 2b). The second mutant transcript lost a 170-bp sequence from exon 24, which led to a frameshift. Expression of a small amount of ABCA12 protein, although mutated, was detected in the granular layer keratinocytes of the patient's epidermis and cultured keratinocytes by immunofluorescent staining [2]. Thus, it is possible that Patient 1 expresses some mutated ABCA12 protein with a partial function. This might be the reason why Patient 1 survived beyond the perinatal and neonatal period and is still alive although this might also be in part due to the prompt oral retinoid treatment.

Patient 2 carried a maternal missense mutation p.Gly1179Arg on the other locus (Fig. 1h). To confirm the presence of the mutation p.Gly1179Arg in Patient 2, we performed restriction enzyme digestion analysis using *Bcl*I (NEW ENGLAND BioLabs). Restriction enzyme digestion of PCR products was carried out according to the manufacture's protocols. The 255-bp PCR products from wild type alleles were not digested by *Bcl*I, although the PCR products from the allele with the mutation p.Gly1179Arg were digested into 173- and 82-bp fragments. The father's PCR product after *Bcl*I digestion showed a single 255-bp band, which indicated he had only normal alleles. In contrast, the PCR product after *Bcl*I digestion from the mother of Patient 2 showed 255-, 173- and 82-bp bands, which indicated that she was heterozygous for the p.Gly1179Arg missense mutation (supplementary Fig. S1). This mutation was reported in a

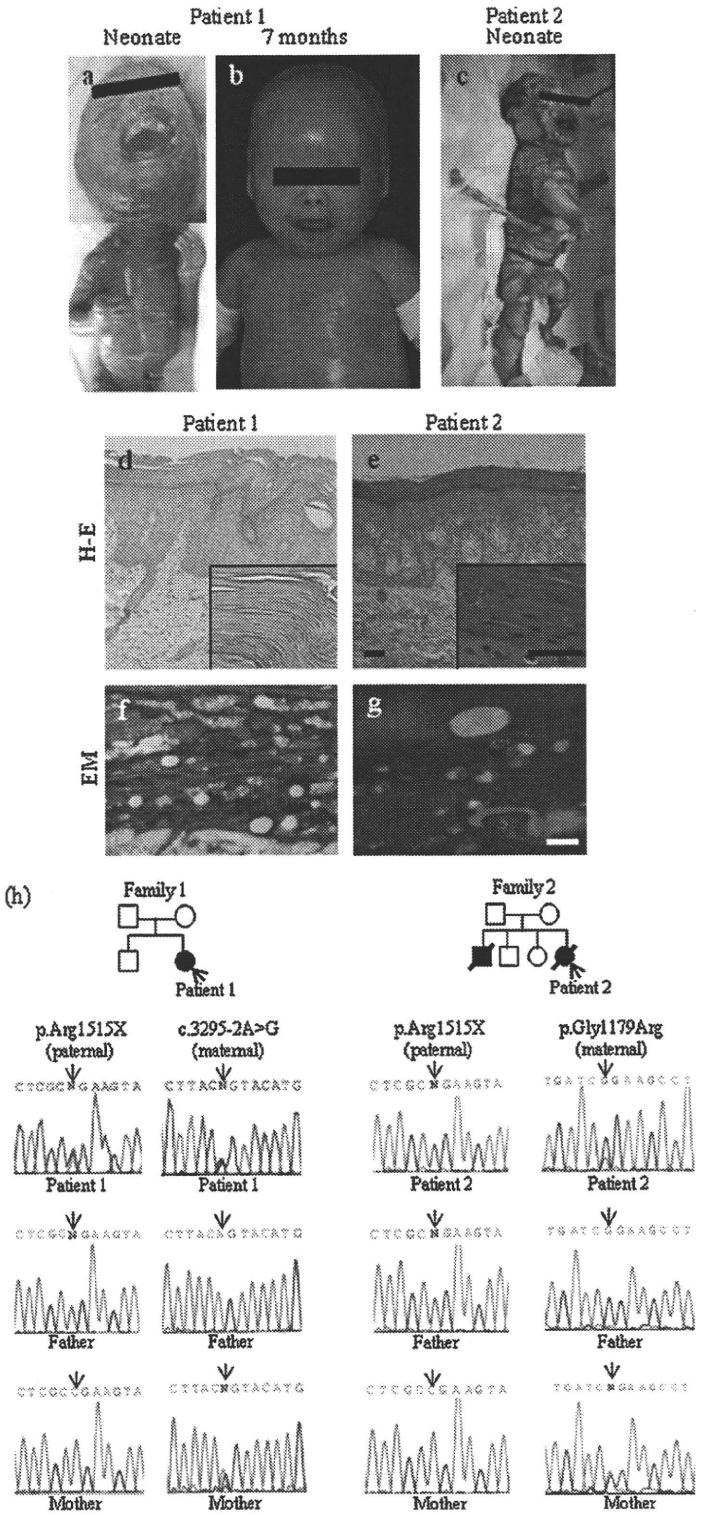
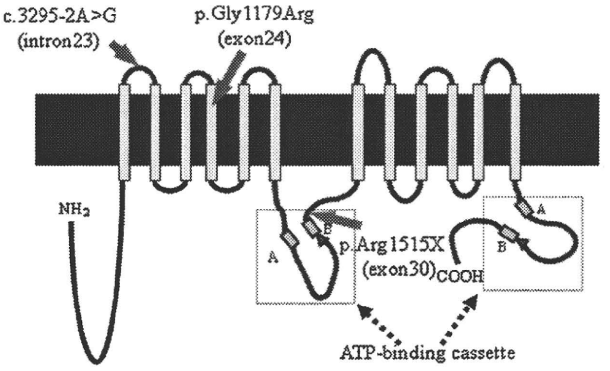


Fig. 1. (a–c) Clinical features of HI patients. Patient 1 showed the typical clinical phenotype of HI during the neonatal period, including the face and trunk (a). Her clinical symptoms remarkably improved at 7 months of age (b). Patient 2 showed more serious symptoms with thick plate-like scales and skin fissures in the neonatal period (c) and lived until the age of 5 months. (d–g) Histological features of the skin lesions of HI patients. Skin biopsies showed thick stratum corneum in both patients. Bars, 50 μm (d and e). In Patient 2, parakeratosis were observed (e, inset). By electron microscopy, abnormal variously sized lipid droplets had accumulated in the cornified cells of both patients' epidermis. Bars, 200 nm (f and g). (h) Families with HI and *ABCA12* mutations. Patient 1 was a compound heterozygote for two *ABCA12* mutations, a novel nonsense mutation p.Arg1515X and a recurrent splice site mutation c.3295-2A>G, and both her parents were heterozygous carriers. Patient 2 harboured two *ABCA12* mutations, p.Arg1515X and p.Gly1179Arg, and both her parents were heterozygous carriers of these defects.



c.3295-2A>G: 1099_1101delYMK

Homo sapiens	1089	VYEKDLRLHEYMKMMGVNSCSHF 1111
Rattus norvegius		VYEKDLRLHEYMKMMGVNSCSHF
Mus musculus		VYEKDLRLHEYMKMMGVNSCSHF
Gallus gallus		VQEKDLRLYEYMKMMGVNASSHF
Danio rerio		VHERELRLHEYMKMMGVNPISHF

p.Gly1179Arg

Homo sapiens	1165	ISVFFNNTNIAALIGSLIYIIAFFPFIVL 1193
Rattus norvegius		ISVFFNNTNIAALIGSLIYVIAFFPFIVL
Mus musculus		ISVFFNNTNIAALIGSLIYVIAFFPFIVL
Gallus gallus		ISVFFNNTNIAALVGSLVYILTFFPFIVL
Danio rerio		VSSFFDKTNIAGLSGSLIYVISFFPFIVL

Fig. 2. (a) Structure of ABCA12 protein and the three mutations in present HI families. Dark blue area, cell membrane; bottom of dark-blue area, cytoplasmic surface. Note the mutation shared between the two patients is a truncation mutation in the first ATP-binding cassette (p.Arg1515X). The other mutation in Patient 2 is just a missense mutation in the first cluster of transmembrane domains (p.Gly1179Arg). (b) ABCA12 amino acid sequence alignment shows the level of conservation in diverse species of the amino acids, 1099_1101delYMK and p.Gly1179Arg (red characters).

Laotian family [6]. The glycine 1179 is a highly conserved amino acid residue (Fig. 2b) located in the first transmembrane ABCA12 domain (Fig. 2a), and this mutation substitutes an uncharged polar glycine residue for a positively charged arginine residue. The presence of these mutations was excluded in 100 alleles of 50 normal unrelated Japanese individuals.

Determinants of genotype/phenotype correlations resulting from *ABCA12* mutations, typically demonstrate that homozygotes or compound heterozygotes with truncation *ABCA12* mutations lead to an HI phenotype. Only a few exceptional cases have been reported such as the present case. The mutation p.Gly1179Arg might result in major loss of ABCA12 function and/or structure, leading to the severe phenotype in Patient 2.

Recently, long-term survival of patients with HI has been more frequently observed and documented [7,8]. The clinical symptoms of Patient 1 showed a remarkable improvement during infancy. In contrast, the symptoms of Patient 2 did not improve, and she died at the age of 5 months. The marked difference in the clinical severity of the two patients indicated that the p.Gly1179Arg has far bigger deleterious functional effects than c.3295-2A>G. The present study clearly demonstrates that some missense *ABCA12* mutations within highly conserved transmembrane regions are able to cause drastic changes in protein structure and function, leading to severe phenotypes, similar to truncation mutation patients. Further accumulation of similar cases is needed to confirm genotype/phenotype correlation in *ABCA12* mutations, especially in studies involving missense mutations underlying HI.

Acknowledgments

We thank Dr. James R. McMillan for proofreading the manuscript. This work was supported in part by a grant-in-aid from the Ministry of Education, Science, Sports and Culture of Japan (Kiban B 20390304: to M.A.), a grant from Ministry of Health, Labour and Welfare of Japan (Health and Labour Sciences Research Grants; Research on Intractable Disease: H22-177: to M.A.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jdermsci.2010.11.010.

References

[1] Akiyama M. Harlequin ichthyosis and other autosomal recessive congenital ichthyoses: the underlying genetic defects and pathomechanisms. J Dermatol Sci 2006;42:83–9.
[2] Akiyama M, Sugiyama-Nakagiri Y, Sakai K, McMillan JR, Goto M, Arita K, et al. Mutations in ABCA12 in harlequin ichthyosis and functional rescue by corrective gene transfer. J Clin Invest 2005;115:1777–84.
[3] Kelsell DP, Norgett EE, Unsworth H, Teh MT, Cullup T, Mein CA, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet 2005;76:794–803.
[4] Akiyama M. ABCA12 mutations and autosomal recessive congenital ichthyosis: a review of genotype/phenotype correlations and of pathogenetic concepts. Hum Mutat 2010;31(July):1090–6.
[5] Lefèvre C, Audebert S, Jobard F, Bouadjar B, Lakhdar H, Boughdene-Stambouli O, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. Hum Mol Genet 2003;12:2369–78.
[6] Thomes AC, Cullup T, Norgett EE, Hill T, Barton S, Dale BA, et al. ABCA12 is the major harlequin ichthyosis gene. J Invest Dermatol 2006;126:2408–13.
[7] Akiyama M, Sakai K, Sato T, McMillan JR, Goto M, Sawamura D, et al. Compound heterozygous ABCA12 mutations including a novel nonsense mutation underlie harlequin ichthyosis. Dermatology 2007;215:155–9.
[8] Akiyama M, Sakai K, Wolff G, Hausser I, McMillan JR, Sawamura D, et al. A novel ABCA12 mutation 327delT causes harlequin ichthyosis. Br J Dermatol 2006;155:1064–6.

H. Umemoto[a,b]
[a]*Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[b]*Department of Oral Diagnosis and Oral Medicine, Hokkaido University Graduate School of Dental Medicine, Sapporo, Japan*

M. Akiyama[a,b,*]
[a]*Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[b]*Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

T. Yanagi
K. Sakai
Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Y. Aoyama
Department of Dermatology, Okayama University Graduate School of Medicine, Okayama, Japan

A. Oizumi
Y. Suga
Department of Dermatology, Juntendo University School of Medicine, Urayasu Hospital, Urayasu, Japan

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/j.1346-8138.2010.01110.x

Journal of Dermatology 2011; **38**: 91–93

LETTER TO THE EDITOR

Dermoscopic features in a case of dyschromatosis symmetrica hereditaria

Dear Editor,

Dyschromatosis symmetrica hereditaria (DSH) is an autosomal dominant pigmentary genodermatosis caused by a mutation in *ADAR1*.[1] It is characterized by the concomitant presence of hyperpigmented and hypopigmented macules on the dorsal hands and feet.[2] The precise pathogenesis is uncertain.[2] Using dermoscopy, we found extraordinary features, which had not been described previously.

A 24-year-old Japanese man presented with a persistent pigment anomaly. Physical examination revealed a mixture of oval or round, hyperpigmented and pigmented spots 1–7 mm in diameter and irregularly shaped hypopigmented macules on the dorsal hands and feet (Fig. 1a). On the face, he had small, freckle-like hyperpigmented spots. The consanguinities had no such pigmentations. To verify the diagnosis precisely, a genetic study was performed as described previously.[3] A novel two-nucleotide deletion mutation (c.1096–1097delAA, p.K366fs) was identified and reported.[4]

We applied dermoscopy to the hyper- and hypopigmented macules on the dorsal hands. In the hyperpigmented macule, round and variously pigmented spots 0.5–1.5 mm in diameter were connected to each other, producing oval hyperpigmented macules (Fig. 1b). Interestingly, the rounded spots showed a variety of pigmented appearances, including reticulated hyperpigmented spots, diffuse pigmentation with hyperpigmented dots, reticulate pigmented spots, monotonous pigmented spots, reticulated hypopigmented spots and monotonous hypopigmented spots (Fig. 1b). The monotonous pigmented spots bore a resemblance to the dermoscopic appearance of the normal skin (Fig. 1b). In the hypopigmented lesions, round and pigmented independent spots 0.5–1.5 mm in diameter were sparsely distributed (Fig. 1c). The rounded spots showed various pigmented appearances, including reticulated pigmented spots, reticulated and monotonous pigmented spots and monotonous hypopigmented spots (Fig. 1c).

Dermoscopy revealed that the hyperpigmented macules were constructed of connected pigmented spots and that the hypopigmented lesions contained unconnected pigmented spots. The reticular pattern is commonly observed in junctional nevus or lentiginous nevus.[5] The reticulated structure in dermoscopy is known to indicate the presence of rete ridges.[5] Therefore, the monotonous pigmentation may reflect the hyperpigmentation of basal keratinocytes without the formation of rete ridges. We were unable to take a biopsy specimen from this patient and could not evaluate the correlation between the dermoscopic findings and the histopathological appearances. However, dermoscopy indicated that the melanocyte activity and the epidermal–dermal structures may vary in each spot. On the other hand, dermoscopy of ephilis shows uniform pigmentation, lentigo simplex dose a uniform pigmented reticulate network, and solar lentigo dose a faint pigmented reticulate network or uniform pigmentation.[6–8]

The dermoscopic features in DSH are different from those in Dowling–Degos disease (DDD) of the external genitalia, showing multiple hyperpigmented brownish spots with different dimensions characterized by a coarse grid of brown lines over a diffuse light-brown background.[9] In the future, it should be studied whether dermoscopy is useful for the differential diagnoses in related disorders of not only DDD but also acropigmentation reticularis Kitamura, dyschromatosis universalis hereditaria and variants.[9–12]

The *ADAR1* gene encodes adenosine deaminases acting on RNA 1 (ADAR1) which catalyze the conversion of adenosine into inosine in RNA molecules.[13] It is an important post-transcriptional mechanism for

Correspondence: Naoki Oiso, M.D., Ph.D., Department of Dermatology, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: naoiso@med.kindai.ac.jp

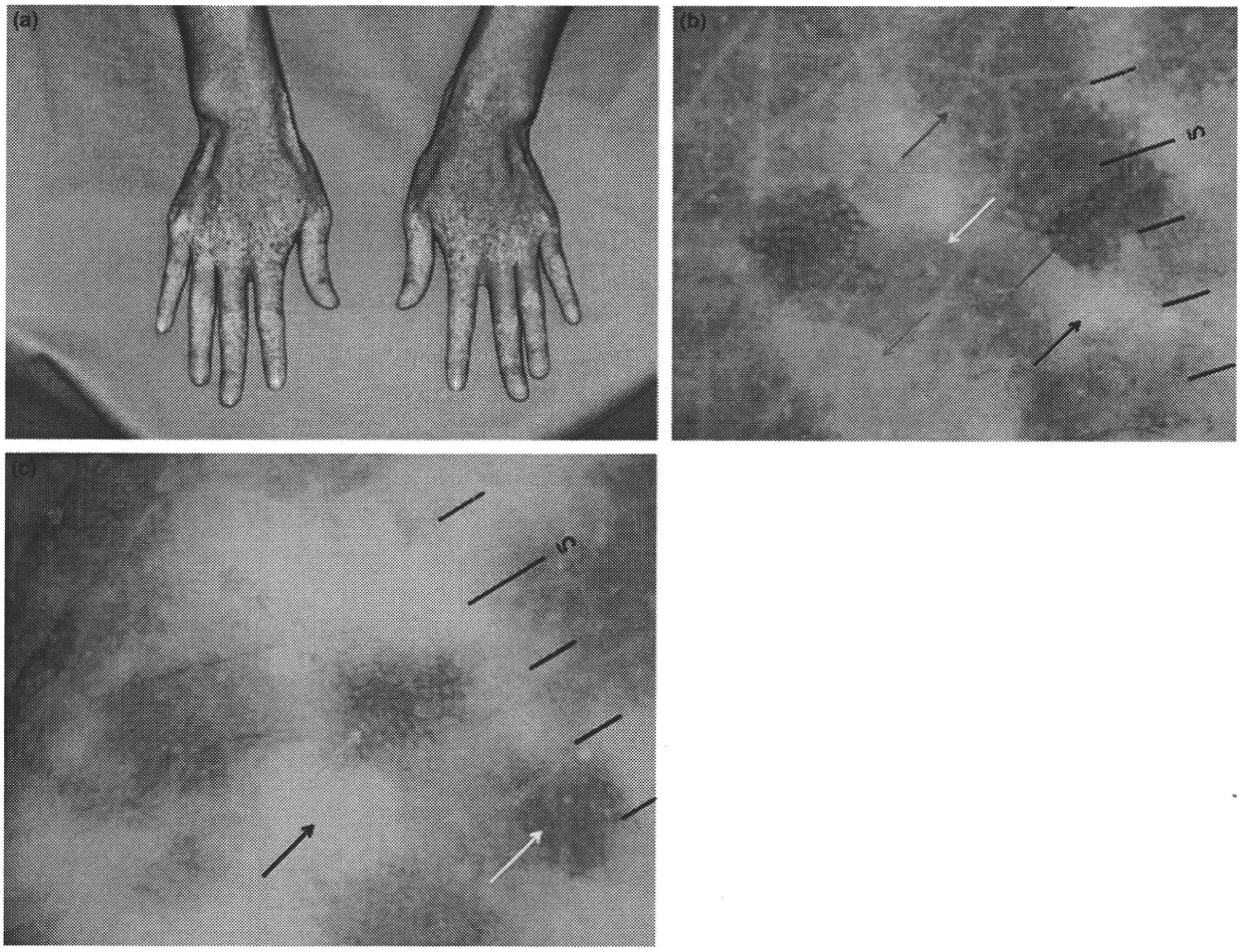


Figure 1. (a) Clinical appearance of oval or round, hyperpigmented and pigmented spots 1–7 mm in diameter and irregularly shaped hypopigmented macules on the dorsal hands. (b) On the dermoscopic examination of the hyperpigmented macule, round and variously pigmented spots 0.5–1.5 mm in diameter were connected, producing oval hyperpigmented macules. The spots were classified as follows: reticulated hyperpigmented spots (red arrow), diffuse pigmentation with hyperpigmented dots (purple arrow), reticulated pigmented spots (green arrow), monotonous pigmented spots (yellow arrow), reticulated hypopigmented spots (blue arrow) and monotonous hypopigmented spots (black arrow). (c) On the dermoscopic examination of the hypopigmented lesion, the round and pigmented independent spots 0.5–1.5 mm in diameter were sparsely distributed. The rounded spots were classified as follows: reticulated pigmented spots (green arrow), reticulated and monotonous pigmented spots (yellow arrow) and monotonous hypopigmented spots (black arrow).

generating transcript diversity.[13] We suppose that dysfunction of ADAR1 induces such various pigment appearances due to the dysregulated post-transcriptional system.

Dermoscopy in DSH showed the different characteristic of each pigmented spot, such as the degree of the pigmentation and the epidermal–dermal structure. We speculated that the pigmented spots have varied melanocyte dysfunction, aberrant melanocyte and keratinocyte interaction, and impaired construction of rete ridges.

Naoki OISO,[1] Ichidai MURATA,[2]
Masahiro HAYASHI,[2] Akinori AMATSU,[1]
Masuki YOSHIDA,[1] Tamio SUZUKI,[2]
Akira KAWADA[1]

[1]*Department of Dermatology, Kinki University Faculty of Medicine, Osaka, and* [2]*Department of Dermatology, Yamagata University School of Medicine, Yamagata, Japan*

REFERENCES

1 Miyamura Y, Suzuki T, Kono M *et al.* Mutations of the RNA-specific adenosine deaminase gene (*DSRAD*) are

involved in dyschromatosis symmetrica hereditaria. *Am J Hum Genet* 2003; **73**: 693–699.
2 Kondo T, Suzuki T, Mitsuhashi Y *et al.* Six novel mutations of the *ADAR1* gene in patients with dyschromatosis symmetrica hereditaria: histological observation and comparison of genotypes and clinical phenotypes. *J Dermatol* 2008; **35**: 395–406.
3 Suzuki N, Suzuki T, Inagaki K *et al.* Mutation analysis of the *ADAR1* Gene in dyschromatosis symmetrica hereditaria and genetic differentiation from both dyschromatosis universalis hereditaria and acropigmentatio reticularis. *J Invest Dermatol* 2005; **124**: 1186–1192.
4 Murata I, Hayashi M, Hozumi Y *et al.* Mutation analysis of patients with dyschromatosis symmetrica hereditaria: five novel mutations of the *ADAR1* gene. *J Dermatol Sci* 2010; **58**: 218–220.
5 Zalaudek I, Docimo G, Argenziano G. Using dermoscopic criteria and patient-related factors for the management of pigmented melanocytic nevi. *Arch Dermatol* 2009; **145**: 816–826.
6 Soyer HP, Argenziano G, Ruocco V *et al.* Dermoscopy of pigmented skin lesions (Part II). *Eur J Dermatol* 2001; **11**: 483–498.
7 Zaballos P, Rodero J, Pastor L *et al.* Dermoscopy of lichenoid regressing solar lentigines. *Arch Dermatol* 2008; **144**: 284.
8 Oiso N, Amatsu A, Kawada A. Hyperpigmented spots within and partly around a hypopigmented macule. *Int J Dermatol* (in press).
9 Massone C, Hofmann-Wellenhof R. Dermoscopy of Dowling-Degos disease of the vulva. *Arch Dermatol* 2008; **144**: 417–418.
10 Batycka-Baran A, Baran W, Hryncewicz-Gwozdz A *et al.* Dowling-Degos disease: case report and review of the literature. *Dermatology* 2010; **220**: 254–258.
11 Oiso N, Tsuruta D, Imanishi H *et al.* Spotted hyperpigmentation: disfigured melanosomes in melanocytes and keratinocytes. *J Eur Acad Dermatol Venereol* 2008; **22**: 876–878.
12 Oiso N, Tsuruta D, Ota T *et al.* Spotted and rippled reticulate hypermelanosis: a possible variant of Dowling-Degos disease. *Br J Dermatol* 2007; **156**: 196–198.
13 XuFeng R, Boyer MJ, Shen H *et al.* ADAR1 is required for hematopoietic progenitor cell survival via RNA editing. *Proc Natl Acad Sci USA* 2009; **106**: 17763–17768.

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/j.1346-8138.2010.00953.x

Journal of Dermatology 2011; **38**: 173–178

CASE REPORT

Dystrophic epidermolysis bullosa pruriginosa of elderly onset

Masahiro HAYASHI,[1,2] Masakazu KAWAGUCHI,[1] Yutaka HOZUMI,[1] Hajime NAKANO,[3] Daisuke SAWAMURA,[3] Tamio SUZUKI[1]

[1]*Department of Dermatology, Yamagata University School of Medicine, Yamagata,* [2]*Division of Dermatology, Yamagata Prefectural Shinjo Hospital, Shinjo, and* [3]*Department of Dermatology, Hirosaki University School of Medicine, Hirosaki, Japan*

ABSTRACT

A 71-year-old man with no family history of skin diseases presented with a 4 month history of recalcitrant pruritic papules and nodules on the lower extremities. He had prurigo-like eruptions with tense bullae on the extensor aspect of his lower extremities with multiple adjacent milia. Toenail dystrophy was observed. Mucous membranes were not affected. Skin biopsy from the shin showed a subepidermal blister with milium. Electron microscopy from lesional and perilesional skin of the leg showed scanty, hypoplastic anchoring fibrils. We detected a heterozygous mutation in the *COL7A1* gene, a G-to-A substitution in exon 87 (c.6859G>A; p.Gly2287Arg). Thus, the clinicopathological and molecular findings supported a diagnosis of dystrophic epidermolysis bullosa pruriginosa. Assessment of other relatives was not feasible. To the best of our knowledge, this is the oldest clinical onset of this unusual variant of dystrophic epidermolysis bullosa reported to date. Why the onset of skin fragility should have occurred so late is not known, but the case serves as a reminder that this particular mechanobullous disease can have a delayed presentation.

Key words: *COL7A1*, dystrophic epidermolysis bullosa pruriginosa, elderly onset, glycine substitution, prednisolone.

INTRODUCTION

Dystrophic epidermolysis bullosa pruriginosa (DEB-Pr) (Online Mendelian Inheritance in Man 604129) is a rare variant of DEB characterized by prominent pruritus, trauma-induced blistering, nail dystrophy, and pruritic prurigo-like and/or lichenoid lesions with milia. McGrath *et al.* initially reported eight cases of DEB-Pr and defined the entity.[1] Although autosomal dominant, recessive and sporadic inheritance patterns have been reported, most cases are dominant. As for all forms of DEB, the molecular pathology involves mutations in the type VII collagen gene, *COL7A1* (NM_000094.3), which encodes a 2944 amino acid protein, the main component of anchoring fibrils.[2] In many cases, the clinical manifestations of DEB-Pr will be evident within the first decade or even in infancy; however, in some cases they may be delayed until the third decade or even until patients are in their 50s.[3,4]

Herein, we report a case of sporadic DEB-Pr of elderly onset. To the best of our knowledge, our case is the oldest clinical onset of DEB-Pr reported to date. Although the reason for the variability in the clinical onset of this disease has not been elucidated yet, the emergence of this disease in an elderly subject has important implications for the differential diagnosis of subepidermal blistering diseases in such patients.

CASE REPORT

A 71-year-old man presented with a 4-month history of pruritic erythematous papules on his lower

Correspondence: Masahiro Hayashi, Ph.D., Department of Dermatology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan. Email: CZK11223@nifty.ne.jp

Received 16 January 2010; accepted 17 March 2010.

extremities. He was treated with a topical steroid and oral antihistamines; however, the number of pruritic papules and nodules gradually increased. He had no family history of skin disease and his parents were not consanguineous. Neither his parents, siblings nor two sons (42 and 49 years old) had skin complaints. He suffered from mild diabetes mellitus and benign prostate hyperplasia and had been taking anti-diabetic and herbal medicine for 1 and 2 years, respectively. Although the topical steroid and oral antihistamines provided some symptom relief, scratching and trauma induced tense bullae and pruritic prurigo-like lesions that gradually appeared mainly on the lower extremities (Fig. 1a). Multiple milia developed following blister re-epithelialization (Fig. 1b,c). He had toenail dystrophy on all toes (Fig. 1d), while his fingernails were intact. Although he had noticed toenail dystrophy in his early teens, it did not cause any inconvenience to him and he had sought no treatment for this. The mucous membranes were not affected. A skin biopsy from the leg revealed dermal–epidermal blister formation with mild lymphocyte infiltration and some eosinophil infiltration in the upper dermis, along with some milia

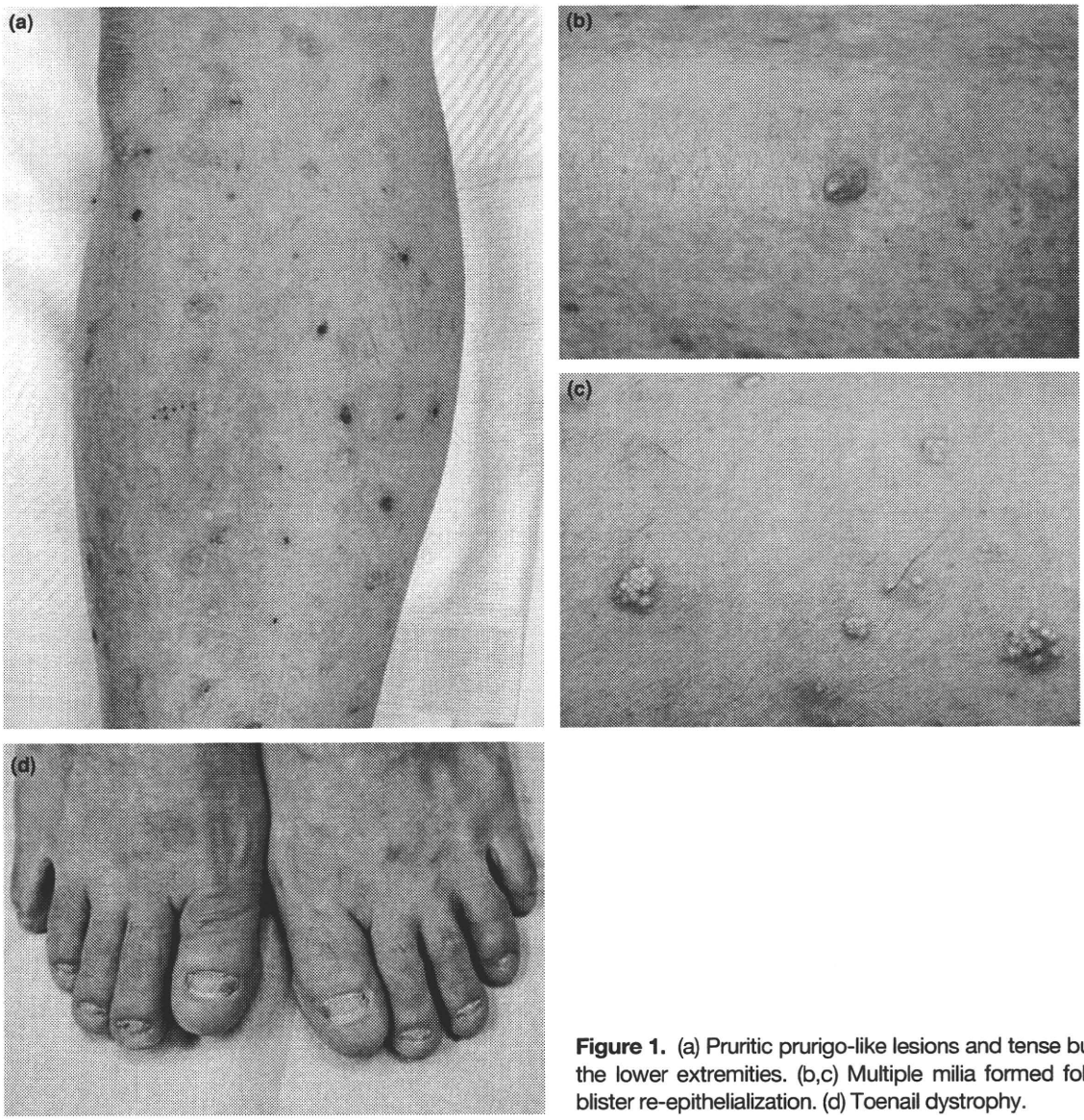


Figure 1. (a) Pruritic prurigo-like lesions and tense bullae of the lower extremities. (b,c) Multiple milia formed following blister re-epithelialization. (d) Toenail dystrophy.

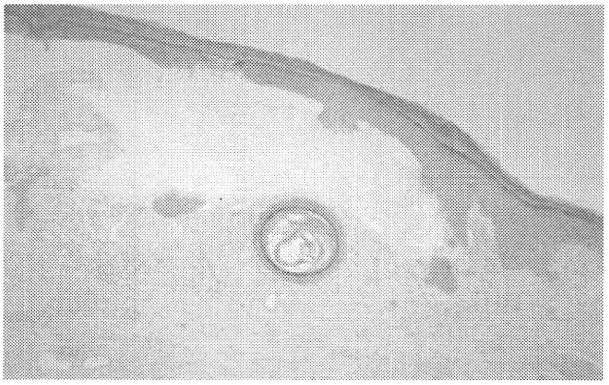


Figure 2. Histopathology of a skin biopsy from the leg. Dermal–epidermal blister formation with mild lymphocytes and partial eosinophil infiltration in the upper dermis and milia (hematoxylin–eosin, original magnification ×100).

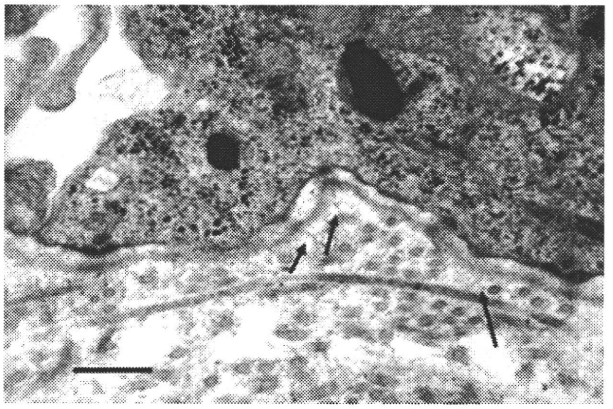


Figure 3. Electron microscopic findings from lesional and perilesional skin of the leg. Anchoring fibrils are scanty and hypoplastic (arrows) (original magnification ×40 000; scale bar, 0.5 μm).

(Fig. 2). Direct immunofluorescence (DIF) showed no immunoglobulin (Ig) or complement deposition at the basement membrane zone. Blood cell count and liver and renal function were all within normal limits. Serum IgE, ferritin and thyroid function were also within normal limits. Immunoblotting studies showed that the patient's serum did not react with any antigen. There were no abnormal findings on chest X-ray, computed tomography, electrocardiogram or upper and lower gastrointestinal endoscopy. An underlying disorder that might cause recalcitrant pruritus was not detected. To rule out drug-induced eruption, all of the drugs he was taking were discontinued and replaced with alternative drugs; however, his symptoms did not improve.

Because the results were not consistent with an autoimmune blistering disease, we examined the skin in more detail. Electron microscopy of lesional and perilesional skin of the leg revealed that anchoring fibrils were scanty and hypoplastic (Fig. 3). After informed consent, genomic DNA was extracted from his peripheral blood samples. Amplified DNA revealed a heterozygous mutation in the *COL7A1* gene, a G-to-A substitution in exon 87 (c.6859G>A; p.Gly2287Arg) (Fig. 4). This mutation has been previously reported by Shimizu *et al.*[5] Considering these findings, we diagnosed the patient with DEB-Pr. Oral prednisolone (PSL) 10 mg/day and 4,4-diamino-diphenyl-sulfone (DDS) 75 mg/day were not effective. Subsequently, PSL 30 mg/day was administrated and the pruritus became markedly

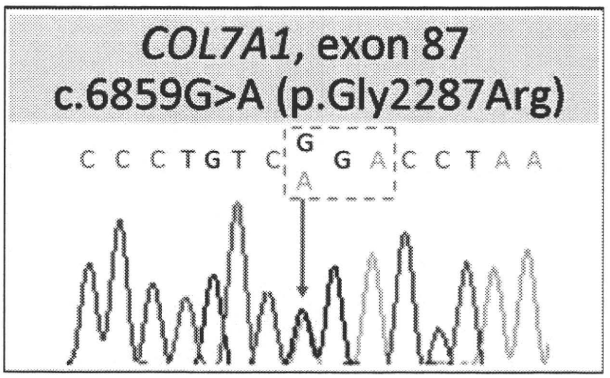


Figure 4. Amplified genomic DNA revealed a heterozygous mutation in the *COL7A1* gene, a G-to-A substitution in exon 87.

less, and no new blisters or prurigo-like lesions were seen. Nevertheless, as the blisters resolved, multiple milia ensued. The dose of PSL was tapered gradually although mild pruritus and a few blisters appeared on the shin when the PSL dose was reduced to 5 mg/day. Topical application of tacrolimus to the prurigo-like lesions also decreased his itching and was considered as effective as oral PSL for symptom control.

DISCUSSION

Dystrophic epidermolysis bullosa pruriginosa was first described by McGrath *et al.*[1] in 1994. It is a rare clinical variant of DEB, characterized by marked

Table 1. Summary of DEB-Pr patients with onset later than 20 years of age

Case No.	Age/Sex	Age at onset of DEB-Pr	Inheritance	Clinical features	Nail dystrophy	Mutation	Complications and past medical history	Treatment	Reference
1	72/M	71	Sporadic	Prurigo-like lesions and blisters with milia of bilateral legs	+	Exon 87 c.6859G>A (p.Gly2287Arg)	Diabetes and prostate hyperplasia	PSL 30 mg/day	Our case
2	34/F	29	Dominant	Pruritic, lichenoid plaques with milia	−	Exon 110 c.8137G>C (p.Gly2713Arg)	Not described	Not described	3
3	27/F	20	Dominant	Prurigo-like papules and milia of pretibial area	+	Exon73 c.6082G>A (p.Gly2028Arg)	Not described	Not described	7
4	44/F	39	Dominant	Pruritus, linear scratching lesions and hyperkeratotic, lichenoid lesions confluent into larger plaques on legs and feet	+	Exon 59 c.5264G>A (p.Gly1755Asp)	Not described	Not described	6
5	39/F	38	Dominant	Pruritus, nodular reddish prurigo-like lesions on left elbow and wrists	+	c.6900 + 4A>G	Not described	Not described	6
6	37/F	38	Dominant	Pruritus, linear scratching lesions and hyperkeratotic lichenoid lesions confluent into large gray-brown plaques on legs and feet	−	c.6900 + 2delTGAT	Not described	Not described	6
7	58/F	53	Recessive	Blistering, excoriated nodules and violaceous scars on lower legs, ankles and elbows	+	Exon 110 c.8206G>A (p.Glu2736Lys)	Diabetes and thyroid cancer	Not described	4
8	52/F	Twenties	Dominant	Intense pruritic blisters on lower legs and extensor surface of both arms	−	Exon 92 c.7097G>T (p.Gly2366Val)	Not described	Not described	8
9	52/F	25	Dominant	Pruritic blisters provoked by scratching on back, nape of the neck, elbows, and both shins	−	Exon 86 c.6752G>A (p.Gly2251Glu)	Subtotal thyroidectomy	Not described	9
10	29/F	27	Sporadic	Multiple lichenified violaceous papules, linear scarring and crusts on extensor sides of feet, lower extremities and elbows	+	Exon 110 c.8137G>C p.Gly2713Arg	Healthy	Topical corticosteroids (not effective)	10

DEB-Pr, Dystrophic epidermolysis bullosa pruriginosa; PSL, prednisolone.

pruritus, trauma-induced blistering, especially on the extensor aspect of the leg, nail dystrophy, prurigo-like lesions and multiple milia. DEB is caused by mutations in the *COL7A1* gene encoding type VII collagen, resulting in a reduced number or disorganization of anchoring fibrils. In DEB-Pr, mainly glycine substitutions have been reported.[6] The onset of clinical symptoms of DEB-Pr is typically during the first decade or even in infancy; however, in some cases clinical onset may be delayed until later in life.[3,4] From these unique clinical features, various differential diagnoses may be considered, such as prurigo nodularis, lichen planus and dermatitis artefacta.

Initially, our patient had pruritic papules and nodules mainly on the leg, which were then followed by tense bullae. Milia formation was seen after the tense bullae re-epithelialized. Our differential diagnoses included pemphigoid nodularis, prurigo nodularis, epidermolysis bullosa acquisita, DEB-Pr and a drug-induced eruption. We ruled out autoimmune blistering disease due to the results of DIF and immunoblotting analysis. Prurigo nodularis usually does not form blisters or milia. Discontinuation of the patient's medication had no clinical impact. However, the combination of the clinical features, the decreased anchoring fibrils on electron microscopy and the detection of the *COL7A1* gene led to a diagnosis of DEB-Pr. Regrettably, we could not acquire informed consent for genetic analysis from his sons; this information would be valuable for knowing whether they might also be at risk for expressing the disorder.

A summary of patients with DEB-Pr with onset later than 20 years of age is shown in Table 1.[3,4,6–10] Of note, there is a female preponderance for all late onset DEB-Pr cases, aside from our patient; the reason for this is unclear. Although the factors responsible for the variability in the time of clinical onset of DEB-Pr have not been elucidated yet, the recognition of this disease having such a late onset adds to the differential diagnosis of subepidermal blistering in elderly subjects.

Dystrophic epidermolysis bullosa pruriginosa has a wide clinical spectrum. In different pedigrees, patients with the same glycine substitution mutation may show clinical heterogeneity.[11] With regard to the pruritus, some DEB-Pr patients have elevated serum IgE and/or atopy,[3,8] but other possible associations such as functional gene promoter polymorphisms in the matrix metalloproteinase-1 (*MMP-1*), which can degrade type VII collagen,[12] and loss-of-function mutations in filaggrin (*FLG*)[4] have not improved clinicopathological understanding of disease mechanisms in DEB-Pr.

Shimizu *et al.*[5] reported a DEB pedigree with the *COL7A1* mutation p.Gly2287Arg, the same mutation as in our case. Their patients showed only nail dystrophy restricted to the great toes and did not show any signs of skin fragility. They determined that this mutation may lead to a very mild phenotype of DEB that might be overlooked. Our patient noticed toenail dystrophy in his early teens, but it was approximately 60 years more before the pruritic eruptions and cutaneous manifestations emerged. Thus, it is likely that our patient has had lifelong dominant DEB, which for most of his life only manifested as nail dystrophy, similar to the cases reported by Shimizu *et al.*[5] However, with the development of pruritus and blistering, the diagnosis evolved to DEB-Pr. Our observations therefore have important implications for the accuracy of genotype-phenotype correlation in DEB and also highlight the potential significance of pruritus in patients with DEB.

The aims of treatment for DEB-Pr are to ease the pruritus and to suppress the scratching activity that leads to the formation of blisters and/or prurigo-like lesions; however, no universally successful treatment has been established. Recent studies have described the efficacy of topical tacrolimus (as we also observed in our patient), systemic cyclosporine and thalidomide.[13–15] McGrath *et al.*[1] reported that treatment with a systemic corticosteroid 10–30 mg/day up to 2 months did not appear to be effective, whereas in our case, oral PSL 30 mg/day was effective and improved the patient's symptoms. We therefore advocate use of topical tacrolimus and a higher dose PSL as potentially useful treatment options for DEB-Pr.

ACKNOWLEDGMENT

The authors are grateful to Professor Takashi Hashimoto (Department of Dermatology, Kurume University) for carrying out the serum immunoblotting analysis and Professor John A. McGrath

(St John's Institute of Dermatology, King's College London) for kind advice on this manuscript.

REFERENCES

1 McGrath JA, Schofield OM, Eady RA. Epidermolysis bullosa pruriginosa: dystrophic epidermolysis bullosa with distinctive clinicopathological features. *Br J Dermatol* 1994; **130**: 617–625.

2 Christiano AM, Greenspan DS, Lee S, Uitto J. Cloning of human type VII collagen. Complete primary sequence of the alpha 1(VII) chain and identification of intragenic polymorphisms. *J Biol Chem* 1994; **269**: 20256–20262.

3 Mellerio JE, Ashton GH, Mohammedi R *et al.* Allelic heterogeneity of dominant and recessive COL7A1 mutations underlying epidermolysis bullosa pruriginosa. *J Invest Dermatol* 1999; **112**: 984–987.

4 Schumann H, Has C, Kohlhase J, Bruckner-Tuderman L. Dystrophic epidermolysis bullosa pruriginosa is not associated with frequent *FLG* gene mutations. *Br J Dermatol* 2008; **159**: 464–469.

5 Shimizu H, Hammami-Hauasli N, Hatta N, Nishikawa T, Bruckner-Tuderman L. Compound heterozygosity for silent and dominant glycine substitution mutations in *COL7A1* leads to a marked transient intracytoplasmic retention of procollagen VII and a moderately severe dystrophic epidermolysis bullosa phenotype. *J Invest Dermatol* 1999; **113**: 419–421.

6 Drera B, Castiglia D, Zoppi N *et al.* Dystrophic epidermolysis bullosa pruriginosa in Italy: clinical and molecular characterization. *Clin Genet* 2006; **70**: 339–347.

7 Murata T, Masunaga T, Shimizu H *et al.* Glycine substitution mutations by different amino acids in the same codon of *COL7A1* lead to heterogeneous clinical phenotypes of dominant dystrophic epidermolysis bullosa. *Arch Dermatol Res* 2000; **292**: 477–481.

8 Chuang GS, Martinez-Mir A, Yu HS *et al.* A novel missense mutation in the *COL7A1* gene underlies epidermolysis bullosa pruriginosa. *Clin Exp Dermatol* 2004; **29**: 304–307.

9 Ee HL, Liu L, Goh CL, McGrath JA. Clinical and molecular dilemmas in the diagnosis of familial epidermolysis bullosa pruriginosa. *J Am Acad Dermatol* 2007; **56**: S77–S81.

10 Broekaert SM, Knauss-Scherwitz E, Biedermann T *et al.* Epidermolysis bullosa pruriginosa due to a glycine substitution mutation in the *COL7A1*-gene. *Acta Derm Venereol* 2006; **86**: 556–557.

11 Nakamura H, Sawamura D, Goto M *et al.* The G2028R glycine substitution mutation in *COL7A1* leads to marked inter-familiar clinical heterogeneity in dominant dystrophic epidermolysis bullosa. *J Dermatol Sci* 2004; **34**: 195–200.

12 Almaani N, Liu L, Harrison N *et al.* New glycine substitution mutations in type VII collagen underlying epidermolysis bullosa pruriginosa but the phenotype is not explained by a common polymorphism in the *matrix metalloproteinase-1* gene promoter. *Acta Derm Venereol* 2009; **89**: 6–11.

13 Yamasaki H, Tada J, Yoshioka T, Arata J. Epidermolysis bullosa pruriginosa (McGrath) successfully controlled by oral cyclosporin. *Br J Dermatol* 1997; **137**: 308–310.

14 Ozanic Bulic S, Fassihi H, Mellerio JE, McGrath JA, Atherton DJ. Thalidomide in the management of epidermolysis bullosa pruriginosa. *Br J Dermatol* 2005; **152**: 1332–1334.

15 Banky JP, Sheridan AT, Storer EL, Marshman G. Successful treatment of epidermolysis bullosa pruriginosa with topical tacrolimus. *Arch Dermatol* 2004; **140**: 794–796.