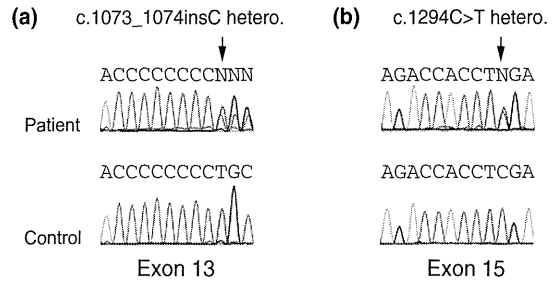

Figure 2 *ANTXR2* sequences of the patient. Sequence data of *ANTXR2* in the patient and a control individual are shown. The arrows indicate the mutation sites, c.1073_1074insC (heterozygous) (a) and c.1294C>T (heterozygous) (b).

tions are needed to conclude a genotype–phenotype correlation between the bi-allelic truncating mutations and hyperpigmentation.

ANTXR2 is a receptor for the anthrax toxin and anthrax toxin induces melanogenesis in melanocytes.[5,6] Thus, hyperpigmentation might be related to abnormal anthrax toxin signal transduction through the mutant ANTXR2 in the present case.

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IgE-independent pathophysiology of severe atopic dermatitis demonstrated in an IgE-deficient patient

Keywords:
Atopic dermatitis
Intrinsic atopic dermatitis
Nonatopic eczema
IgE
Filaggrin

About 20% of patients with the clinical diagnosis of atopic dermatitis (AD) have no IgE-sensitization to food or aeroallergens and have low to normal serum IgE levels, in contrast to archetypal AD patients, who show clinically relevant IgE-sensitization [1,2]. Based on the concept that these two forms of AD are distinct entities, the World Allergy Organization proposed the nomenclature of "atopic eczema" (AE) and "nonatopic eczema" (nonAE) [3]. Alternatively, by borrowing the terminology of asthma classification, many dermatologists apply the terminology of "intrinsic AD" (IAD), to differentiate from IgE-associated AD, which is termed "extrinsic AD" (EAD) [1]. Other terminology, such as non-IgE-associated AD or atopiform dermatitis, has been proposed as well [4]. The different pathophysiologies of AE/EAD and nonAE/IAD have been studied, although the extent to which they share common mechanisms remains unclear. Furthermore, a debate remains on whether IgE plays a pathogenic role in nonAE/IAD patients, because microbial allergen-specific IgEs that are not commonly tested in clinical practice may be detected in the sera of these patients [5]. Here we describe an adult patient with severe AD accompanied by total IgE deficiency, harboring a heterozygous *FLG* mutation.

A 33-year-old Japanese man was referred to our outpatient clinic with itchy eruptions on his whole body. He had a medical history of AD that started in childhood, and he had received left cataract surgery but was otherwise generally healthy. He had no history of asthma or allergic rhinitis. He had no family history of allergic diseases. Physical examination revealed diffuse lichenification and scaly erythema on the whole body. Keratotic papules were grouped on the extremities, and thick, exudative plaques with lichenification were seen on the wrists and ankles (Fig. 1A, B). Dennie–Morgan folds on his lower eyelids and palmar hyperlinearity were evident. A skin biopsy from the abdomen revealed the histological features of chronic eczema (Fig. 1C). Infiltrating cells consisted mostly of lymphocytes, although a few eosinophils and basophils were also seen. He was clinically diagnosed with AD according to the criteria of Hanifin and Rajka [6]. The objective score of atopic dermatitis (OSCORAD) was 78. Laboratory tests revealed hyper-eosinophilia, with a leukocyte count of 12.1×10^3 cells/μL (normal range: $3.9–8.5 \times 10^3$ cells/μL), an eosinophil fraction of 22.0% (normal range: 1–6%), a basophil fraction of 0.6% (normal range: ≤4%), and CCL17 levels elevated to 14,730 pg/mL (normal range: >450 pg/mL). Unexpectedly, the IgE measurement was below 1 IU/mL, i.e., below the detection limit of our assay. Thrice-repeated measurements and a serum dilution test with standard IgE sample demonstrated consistently negative results. Accordingly, food- and aeroallergen-specific IgE was also undetected. IgG was slightly elevated, at 2,076 mg/dL (normal range: 870–1700 mg/dL), and other immunoglobulin subclasses were within normal limits. His serum interleukin (IL)-4 was 11.3 pg/mL (normal range: >6.0 pg/mL), IL-5 was 3.9 pg/mL (normal range: 3.9> pg/mL) and interferon (IFN) γ was 0.1> IU/mL (normal range: >0.1 IU/mL). Flow cytometry analysis demonstrated that populations of $HLA\text{-}DR^+CD3^+$ were increased to 41% (normal range: 5.0–33.0%), reflecting the activation of T cells. Within the $CD4^+$ cells, the Th1/Th2 ratio was 6.3; $IFN\gamma^+IL4^-$ Th1 and $IFN\gamma^-IL4^+$ Th2 cells accounted for 25% and 4.0% of the cells, respectively. $CD4^+CD25^+$ cells accounted for 14.4% of the lymphocyte fraction (normal range: 6.0–21.0%). Laboratory data are summarized in Table 1. Genomic sequencing revealed the heterozygous mutation p.Ser2889X in *FLG* encoding profilaggrin/filaggrin. Treatment with either oral corticosteroid or cyclosporine A brought moderate improvement.

In a recent large population-based cohort study of Swedish teenagers, Johansson et al. proposed that, although nonAE patients had a later onset, a less chronic disease and a less severe disease than AE, AE and nonAE are one disease phenotype [7]. Despite the idea that AE/EAD and nonAE/IAD are entirely distinct entities, several hypotheses give a common pathological basis for these conditions. One possibility is that nonAE/IAD may possess IgEs that are sensitized to unexamined allergens [1,2,5]. However, the present case demonstrates that an IgE-dependent mechanism is indispensable for the establishment of the severe AD phenotype in at least some cases. Another hypothesis is that non-AE/IAD may develop into AE/EAD through IgE sensitization over time [4,8]. In this theory, a common, putative prototypical pathomechanism is hypothesized, with Th2-driven, IgE-dependent mechanisms then further modifying the AE/EAD pathophysiology. Many attempts to elucidate the immunological differences between IAD and EAD have been made, and the evidence has been conflicting [1]. Several studies reported that IAD is more skewed toward Th1 polarity, whereas EAD shows higher levels of Th2 cytokines and chemokines. In the present case, the laboratory test results showed hybrid Th1/Th2 activation with emphasis on Th1, as seen from the Th1-skewed flow cytometry results, and mildly elevated levels of serum IL-4 (Table 1).

Besides revealing the involvement of Th1 and Th2, recent studies have revealed the involvement of the Th17 axis in the formation of these skin lesions. In a recent study using patients' skin, mRNA levels of Th2 cytokines were similarly elevated in both forms of AD, but expression levels of IFNγ, IL-17 and IL-22 were

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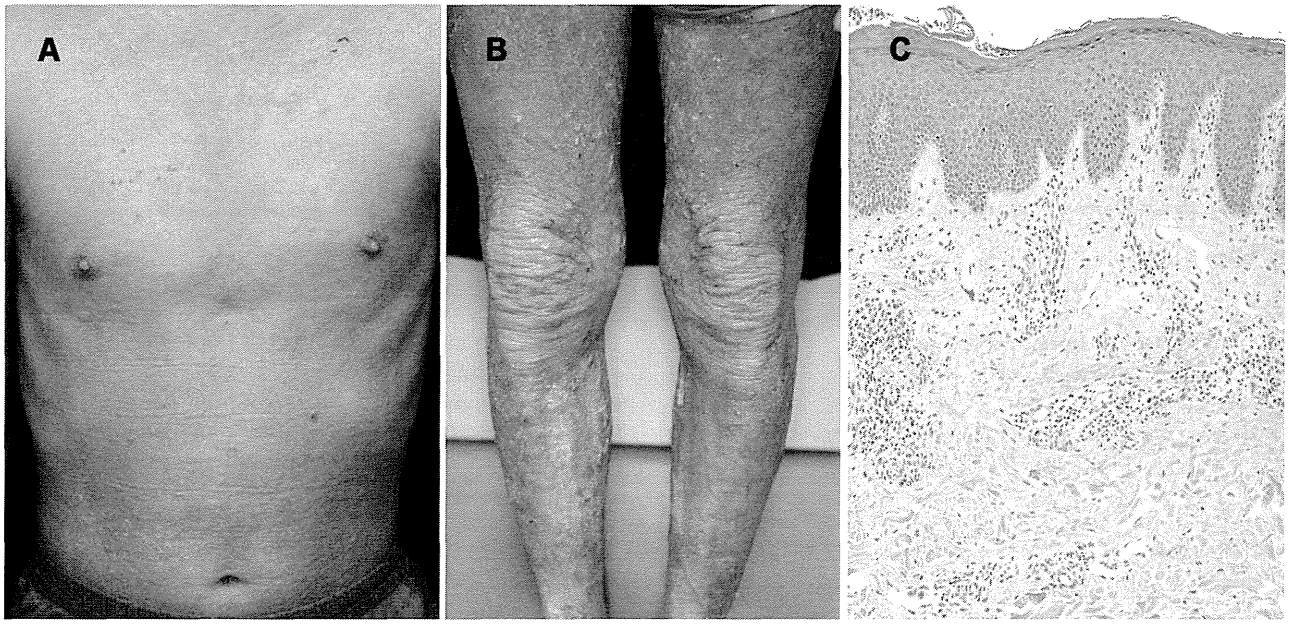

Fig. 1. The present IgE-deficient male patient with severe atopic dermatitis. (A) Clinical picture of the trunk. Diffuse lichenification and erythema are seen. (B) Clinical picture of the legs. Diffuse erythema, lichenification and keratotic papules are seen. (C) Skin biopsy reveals hyperkeratosis, acanthosis and perivascular infiltration of lymphocytes in the dermis (hematoxylin-eosin, original magnification ×200).

significantly more elevated in IAD than in EAD [9]. Thus, although serum IL17A/F levels were not examined in the present case, we speculate that Th17 cells are involved in the pathogenesis of the severe skin manifestations. The Th2 activation, as indicated by elevated CCL17 and IL-4 levels, and the manifestation of strong pruritus in this case prompted us to suspect a possible role of thymic stromal lymphoprotein (TSLP), although we were unable to examine the TSLP levels of the patient's skin lesions.

Selective IgE deficiency is a rare entity, and its cause has not been discovered [10]. Considering that repeated blood tests failed to detect even trace amounts of IgE, we suspect that the patient has a deficient class-switch mechanism, although further genetic analysis is needed to test this hypothesis.

In conclusion, the present case clearly indicates that severe AD manifestations can be established and persist even in the total absence of IgE.

Table 1
Cytokine profile, T cell subsets and clinical features of the present case.

	Present case		(Reference range[a])	IAD[b]	EAD[b]
Serological examinations					
IgE	<1 IU/mL	Low	(220>)	**Low to normal**[c]	High
CCL17	14730 pg/mL	High	(450>)	**High**	**High**
IL-4	11.3 pg/ml	Slightly elevated	(6.0>)	Lower expression	**Higher expression**
IL-5	3.9 pg/ml	Low	(3.9>)	**Lower expression**	Higher expression
IFN-γ	>0.1 IU/mL	Low	(0.1>)	Higher expression	**Lower expression**
Flow cytometry					
$CD4^+$ T cell subsets					
Th1: $IFN\gamma^+/IL4^-$	25%		(NA)		
Th2: $IFN\gamma^-/IL4^+$	4.0%		(NA)		
Th1/Th2	6.3	Th1 > Th2	(NA)	**Th1 ≥ Th2**	Th1 < Th2
Clinical features					
Severity	Severe			Less severe	**More severe**
Disease onset	Early			Later	**Earlier**
Palmar hyperlinearity	Present			Negatively associated	**Positively associated**
Asthma	Absent			**No association**	Increased risk
Allergic sensitization	Absent			**No association**	Increased risk

NA: not applicable.
[a] Reference range at our facility.
[b] Modified from Tokura [1].
[c] Underlined parameters represent resemblance to the present case.

Conflicts of interest

The authors have no conflict of interest to declare.

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SHORT COMMUNICATION

A 45-year-old Woman with Ehlers-Danlos Syndrome Caused by Dermatan 4-*O*-sulfotransferase-1 Deficiency: Implications for Early Ageing

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Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders characterized by joint and skin laxity and tissue fragility (1). Dermatan 4-*O*-sulfotransferase-1 (D4ST1) deficiency, a recently delineated form of EDS caused by bi-allelic loss-of-function mutations in the carbohydrate sulfotransferase 14 gene (*CHST14*), is clinically characterized by multiple congenital malformations (craniofacial abnormalities, multiple congenital contractures, congenital heart/eye/gastrointestinal defects) and progressive fragility-related manifestations (skin hyperextensibility and fragility, large subcutaneous haematomas, recurrent dislocations, progressive skeletal deformities) (2). Biochemical and pathological investigations on patients' skin specimens suggest multisystem fragility caused by impaired assembly of collagen fibrils resulting from dermatan sulphate (DS) depletion in the decorin glycosaminoglycan (GAG) side chain (2). The disorder is currently called "EDS musculocontractural type 1" (MIM#601776) or "D4ST1-deficient EDS" (2). We report here a 45-year-old Japanese woman with the disorder.

CASE REPORT

At birth, the patient had talipes equinovarus, resulting in progressive foot deformities and difficulty walking. She had hyperextensible, easily bruisable, fragile skin. Thus, she was suspected of having general EDS. She presented congenital optic nerve atrophy of the right eye, leading to blindness. Hearing impairment was noted. After arthrodesis for bilateral talipes equinovarus at age 5 years, she was able to walk independently. At age 17, she had a right hip dislocation. At age 18, hair loss occurred on the frontal region. At age 24, she developed bacterial endocarditis, resulting in mitral valve insufficiency, and underwent mitral valvuloplasty. At age 30, she had colon diverticulitis. At age 36, she had retinal detachment, glaucoma and cataract of the left eye. At age 41, she had a left hip joint dislocation, during the reposition of which a large subcutaneous haematoma developed along the left lower leg, resulting in skin necrosis. It was then that she was referred to our department of the hospital for further examination.

At initial examination we diagnosed the patient as having general EDS because of skin hyperextensibility and joint hypermobility. Hydronephrosis and nephrolithiasis, detected at age 40 years, were followed by pyelonephritis at age 44 years. When last seen by us at age 45 years, her height was 147 cm (−2.0 standard deviation (SD)) and her weight was 38 kg (−2.3 SD). She had characteristic facial features, including an asymmetrical shaped face, hypertelorism, short and downslanting palpebral fissures, strabismus, a short nose with hypoplastic columella and a long philtrum with a thin upper lip vermilion; she looked old for her age, with sparse hair on the forehead (Fig. 1a). She had tapering fingers and wrinkled palmar creases (Fig. 1b, c). Her skin was hyperextensible and redundant and her small joints were hypermobile (Fig. 1e, f). Her left lower leg was covered with hypertrophic scars resulting from skin grafts (Fig. 1f). She was unable to walk independently because of progressive foot deformities (Fig. 1f) and she used a walker or wheelchair for mobility. Personal photographs illustrate the patient's physical development over 0–26 years of age (Fig. S1 g–l[1]).

Microscopic investigations of a skin biopsy specimen from the medial side of the arm were performed. Light microscopy revealed the following: fine collagen fibres were predominant in the reticular to the papillary dermis, normally thick collagen bundles were markedly reduced in the reticular dermis (Fig. S2a[1]) and elastic fibres were relatively increased in the dermis (Fig. S2b[1]). Electron microscopy revealed insufficiently assembled collagen fibrils (Fig. S2d[1]).

Direct sequencing of *CHST14* on genomic DNA extracted from her peripheral blood leukocytes revealed 2 compound heterozygous mutations that had both been reported in Japanese patients with EDS caused by D4ST1 deficiency (2): c.626T>C and c.842C>T (p.(Phe209Ser)) and (p.(Pro281Leu)) (Fig. S2e, f[1]). Both mutations of p.F209S and p.P281L were deduced to be probably damaging by PolyPhen-2 and deleterious by SIFT. The diagnosis was confirmed as EDS caused by D4ST1 deficiency.

DISCUSSION

The clinical features and course of this patient, especially the characteristic craniofacial and cutaneous appearance that suggested early ageing, as well as the progressive skeletal, vascular, ocular, and visceral complications, raise the possibility of a relationship between DS depletion and early ageing. Of the 39 patients with the disorder described to date, including the recent series by Janecke et al. (3) and the present patient, 6 were reported to be older than 30 years at their latest publication (3–5). Four of the 5 whose facial photographs were available showed "aged looking" craniofacial and cutaneous appearances, such as sparse hair and progressively wrinkled palmar creases. Three were unable to walk independently due to foot deformities or recurrent large subcutaneous haematomas. Three had gastrointestinal diverticulitis associated with perforation

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2390

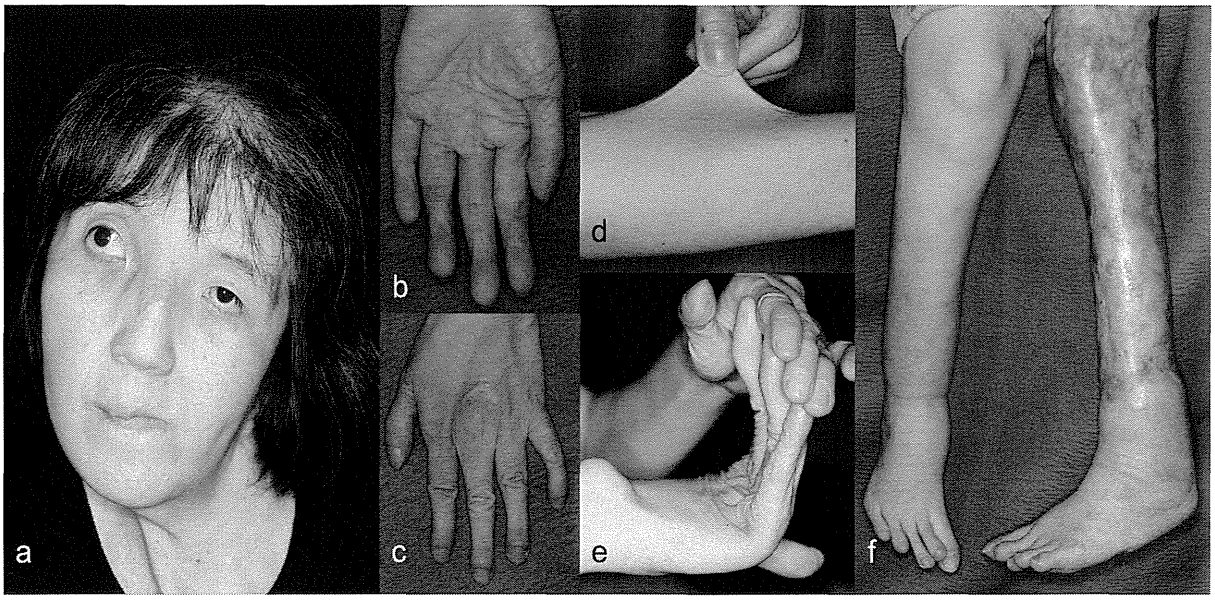

Fig. 1. Clinical photographs at age 45 years. (a) Facial features include an asymmetrical shaped face, hypertelorism, short and downslanting palpebral fissures, strabismus, a short nose with hypoplastic columella and a long philtrum with a thin upper lip vermilion. (b) Wrinkled palmar creases on the left hand. (c) Tapering fingers of the left hand, with clinodactyly. (d) Skin hyperextensibility on the forearm. (e) Joint hypermobility of the fingers. (f) Bilateral foot deformities and scar formation after skin necrosis on the left lower leg. Written permission was obtained from the patient to publish these photographs.

in 2 of the 3, and 2 had (haemo)pneumothorax. Three developed retinal detachment and 1 severe glaucoma, resulting in blindness in 2 of them. One died at age 59 years from intracranial haemorrhage after a fall (5).

Ageing is a natural, continuous process associated with progressive structural, functional, and metabolic changes in various tissues and systems. Parts integral to this process have been shown to be structural and functional alterations in extracellular matrix components, including GAGs (6). Linear age-related declines in plasma DS, chondroitin sulphate (CS), and heparan sulphate/heparin were demonstrated in healthy individuals (7). Furthermore, the progeroid form of EDS was found to be caused by loss-of-function mutations in *B4GALT7* or *B3GALT6*, both encoding galactosyltransferases that form a tetrasaccharide linker region indispensable to the initiation of CS/DS biosynthesis (8–10).

In conclusion, we have described an additional middle-aged patient with EDS caused by D4ST1 deficiency, whose "aged looking" craniofacial and cutaneous appearance and progressive multisystem complications suggest that DS depletion could be involved in early ageing.

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Fig. S1. Time series of clinical photographs of the patient. (g) 0, (h) 1, (i) 5, (j) 10 (k) 18 and (l) 26 years old. Written permission was obtained from the patient to publish these photographs.

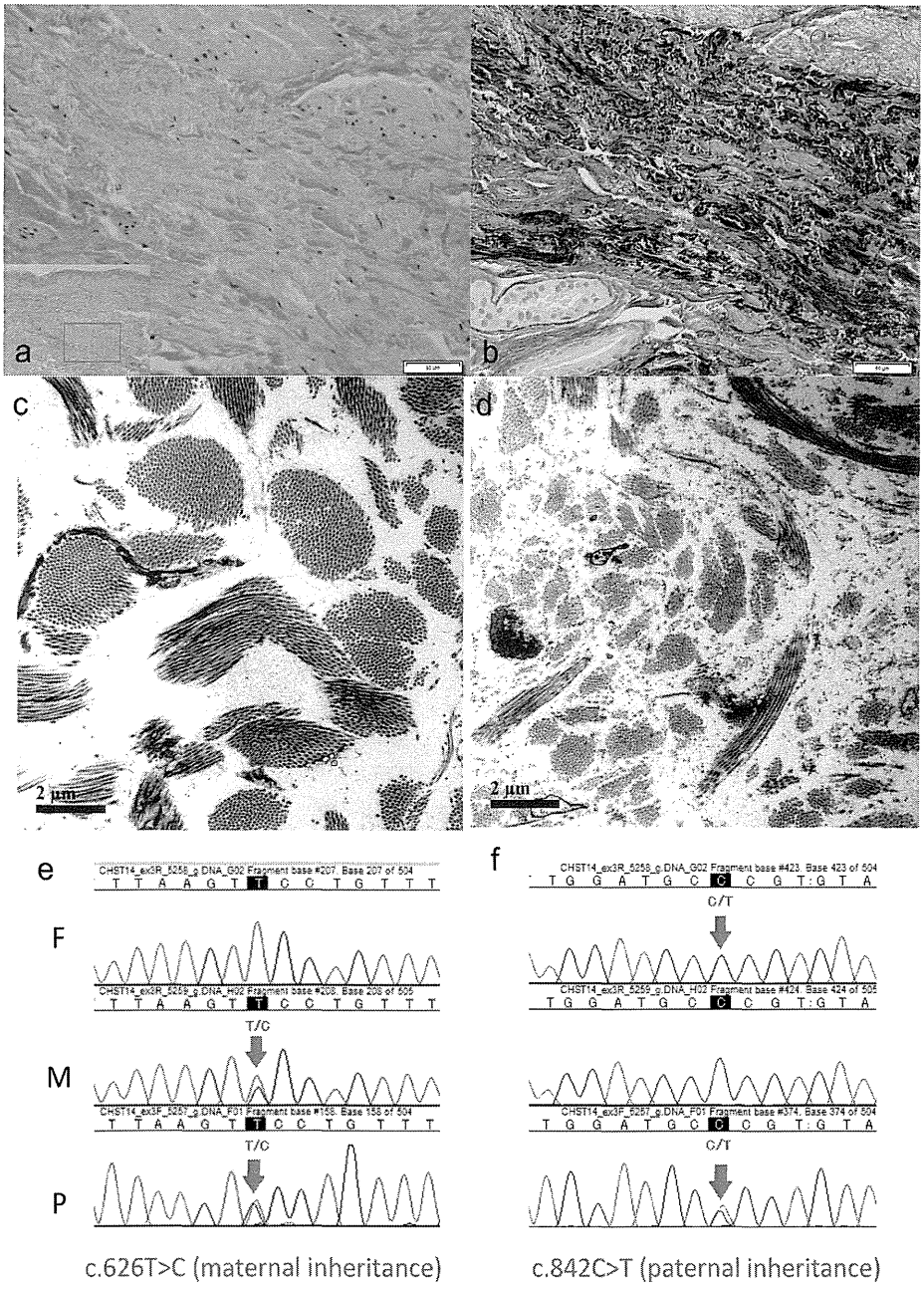

Fig. S2. Pathological examination and molecular investigation. (a, b) Light microscopic findings. A haematoxylin and eosin-stained skin specimen from the patient shows fine collagen fibres to be predominant from the reticular to the papillary dermis, and normally thick collagen bundles in the reticular dermis are markedly reduced (×400) (a). An *elastica* van Gieson-stained skin specimen shows increased elastic fibres in the dermis (×400) (b). (c, d) Electron microscopic findings. Compared with regularly and tightly assembled collagen fibrils in a control specimen (×10,000) (c), the assembly of collagen fibrils is observed to be insufficient in the patient (×10,000) (d). Direct sequencing of *CHST14* on genomic DNA from the patient reveals compound heterozygous mutations (P): c.626T>C (p.Phe209Ser) from her mother (M) and c.842C>T (p.Pro281Leu) from her father (F).

LETTER TO THE EDITOR

A case of epidermolytic ichthyosis showing a very mild phenotype due to a novel tail extension mutation in *KRT10*

Editor

Epidermolytic ichthyosis (EI) is keratinopathic ichthyosis that is characterized by generalized multiple blisters and erosions with erythroderma at birth.[1] EI is caused by autosomal dominant, rarely recessive mutations in the keratin 1 gene (*KRT1*) or the keratin 10 gene (*KRT10*). Here, we report a female EI patient showing an extremely mild phenotype caused by a unique 4-bp nucleotide deletion including a stop codon in *KRT10*.

An 11-year-old Japanese girl who had been born with dry skin mainly on the trunk showed pigmentation on the intertriginous areas with growth. She had not shown erythroderma, blisters or erosions at any time since birth. She had lived in Thailand for 8 years from the age of 2, and the symptoms were relieved during her time in that humid climate. When she returned to Japan at the age of 10, because of its drier climate, the symptoms worsened, particularly in winter.

Symmetrical keratotic lesions were seen mainly on the lateral sides of the trunk, the axillae, the groins and the legs (Fig. 1a–d). The palms and soles were spared, as is often the case with EI patients with *KRT10* mutations. Light microscopy of a skin biopsy specimen revealed hyperkeratosis, papillomatosis and slight acanthosis in the epidermis (Fig. 1e). Vacuolated keratinocytes with prominent clumping of keratohyalin granules, a condition called 'granular degeneration', were seen only in the granular cell layers (Fig. 1f).

Electron microscopy revealed irregularly shaped, compact, clumped keratin filaments in the cytoplasm of keratinocytes in the granular cell layers (Fig. 1g). Before our mutation analysis, the putative diagnosis for the present case was superficial epidermolytic ichthyosis (SEI).

Informed consent and genomic DNA from peripheral blood samples of the patient and her parents were obtained under protocols approved by the Ethics Review Committee of the Nagoya University School of Medicine. Mutation analysis of the coding regions and exon–intron boundaries of *KRT1* and *KRT10* for EI and *KRT2* for SEI was performed by direct sequencing methods using specific primers. The novel heterozygous mutation c.1752_1755delCTAA (p.*585Lysfs*33) was detected in *KRT10* (Fig. 1h). This small deletion of 4 bps including a stop codon in *KRT10* resulted in mutant keratin 10 with an extended tail domain of 32 amino acids longer than the wild type (Fig. 1i). We were unable to find any pathogenic *KRT1* or *KRT2* mutation. The definite diagnosis of EI was made.

Genotype–phenotype correlations in EI are highly complicated. Most pathogenic mutations are missense and in-frame small deletion/insertion mutations localized to the highly conserved 1A helix initiation motif or 2B helix termination motif. These mutations lead to severe EI.[2] Mutations outside the helix initiation/termination motifs, such as one in the L12 linker,[3] have been described in relatively mild cases. However, specific mutations in 2B domain, which showed mild EI, were recently reported.[4,5]

In *KRT1*, mutations in the elongated tail domain were reported in two EI cases, one showing a severe phenotype[6] and the other showing a mild phenotype.[7] Concerning the effects of *KRT1* mutations in the elongated tail domain on the structure of that domain, eight of ten glycine loops in the tail domain were found to be conserved in the above-mentioned mild case. In contrast, only two glycine loops were found to be conserved in the above-mentioned severe patient. Glycine loops in the tail domain of keratins were suggested to be important for the functioning of keratin proteins.[6] The mild, late-onset phenotype of the present case might be due to the fact that all glycine loops of the keratin 10 tail domain were conserved in our case.

It was difficult to differentiate SEI clinically and histopathologically in the present patient. Occasionally, it is not easy to clinically differentiate between severe SEI cases and mild EI patients.[8] Indeed, in the present case, the definite diagnosis of EI was made only after mutation analysis.

In conclusion, our case suggests that a 32 amino acid tail extension of keratin 10 results in a very mild phenotype that is difficult to differentiate from SEI. The present patient further supports the notion that mutation analysis helps us to differentiate between EI and SEI.

The authors thank Ms. Mutsumi Suganuma for their technical help in analysing *KRT1, KRT2, KRT10* mutations.

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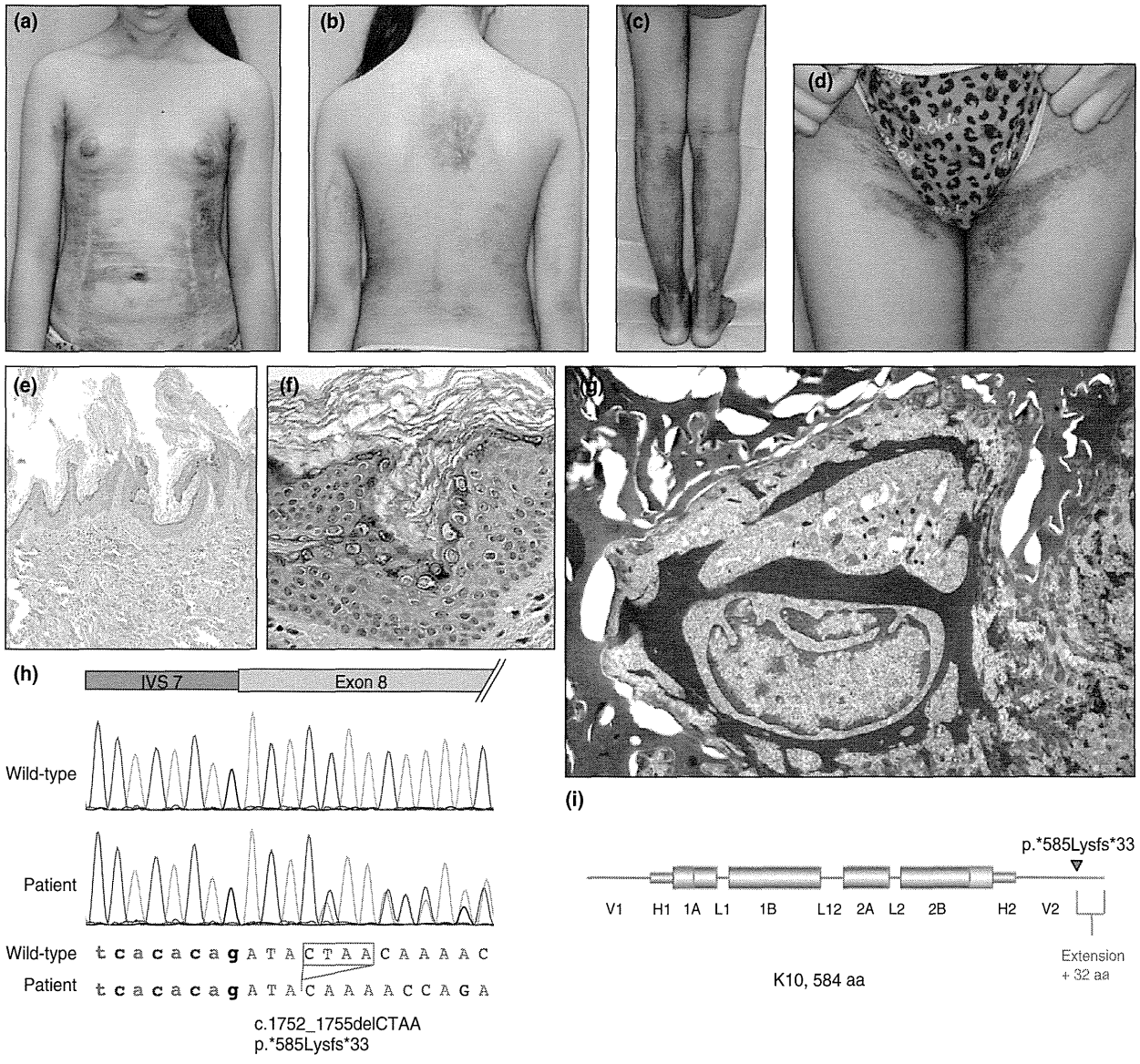

Figure 1 Clinical, histopathological and ultrastructural features of the skin lesions and the causative keratin 10 mutation. (a–d) Symmetrical keratotic lesions are mainly seen on the lateral chest and abdomen (a), on the back and the axillae (b), on the legs (c) and on the groin (d). The lesions are not diffuse but are spotting. The cubital fossa and popliteal fossa are spared. (e) A low-power microphotograph of a skin lesion shows hyperkeratosis and papillomatosis in the epidermis. (f) A high-power microphotograph of a skin lesion reveals vacuolated keratinocytes with prominent clumping of keratohyalin granules, known as 'granular degeneration', in the upper epidermis. The granular degeneration was largely limited to the granular cell layers and did not extend into the spinous layers. (g) Electron microscopy reveals compact clumped keratin filaments in the cytoplasm of a keratinocyte in the granular cell layer. (h) The novel heterozygous deletion mutation c.1752_1755delCTAA (p.*585Lysfs*33) was detected in *KRT10*. (i) A diagram of the K10 protein domain structure and the pathogenic mutation of the present case. The α-helical rod domains encompass domains 1A to 2B, and the major cluster sites for the most pathogenic mutations are localized to the helix boundary motifs at either end of domains 1A (red) and 2B (green). The present mutation, p.*585Lysfs*33, results in a 32 amino acid tail extension.

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SHORT COMMUNICATION

Angiofibroma of Soft Tissue on the Cheek: Diagnosis Confirmed by Gene Rearrangement in *NCOA2*

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Angiofibroma of soft tissue (AFST) was first reported in 2012 (1). AFST is a tumour with a well-defined margin, characterized by angiogenesis and the proliferation of spindle cells. Clinically, AFST is a slow-growing tumour that most commonly occurs on the lower limbs, with a female predilection (1, 2). We report here a case of AFST on the face, which was diagnosed by the detection of gene rearrangement in the nuclear receptor coactivator 2 gene (*NCOA2*).

CASE REPORT

A 50-year-old woman visited a local clinic with a 2-year-history of a slowly growing subcutaneous mass on her left cheek. Palpation revealed a mobile, firm mass, 3 cm in diameter, with a well-defined margin, accompanied by mild tenderness. One year later, the patient underwent incisional biopsy of the mass and was referred to us for further evaluation and treatment. We examined the tumour with magnetic resonance imaging (MRI). The tumour had enlarged from 8 × 10 mm (Fig. 1b, c) to 10 × 25 mm in 12 months; therefore, total excision was performed.

Histopathologically, the tumour was well defined, but un-encapsulated. It was located between the subcutaneous fat tissue and the zygomaticus minor (Fig. 1d–f). It was composed of spindle cells and giant cells, accompanied by a network of proliferating small vessels and myxoid stroma. Around the tumour, there was infiltration of inflammatory cells, mainly lymphocytes. Immunohistochemical investigation found that the tumour was positive for desmin (Fig. 1i) and D2-40, weakly positive for α-smooth muscle actin (α-SMA), partially positive for CD68 (Fig.1 g, h), and negative for CD31, CD34 and S-100. The Ki-67 index was 3%. Differential diagnoses considered were: nodular fasciitis, solitary fibrous tumour and giant cell angiofibroma; however, these were ruled out from the clinical and histopathological findings.

Considering the possibility of AFST, we therefore performed chromogenic *in situ* hybridization (CISH) with paraffin-embedded specimens of the lesion, using a break-apart probe for *NCOA2*, as reported previously (3–5). Some spindle cells were positive for gene rearrangement in *NCOA2* (Fig. 1j). This finding led to a diagnosis of AFST.

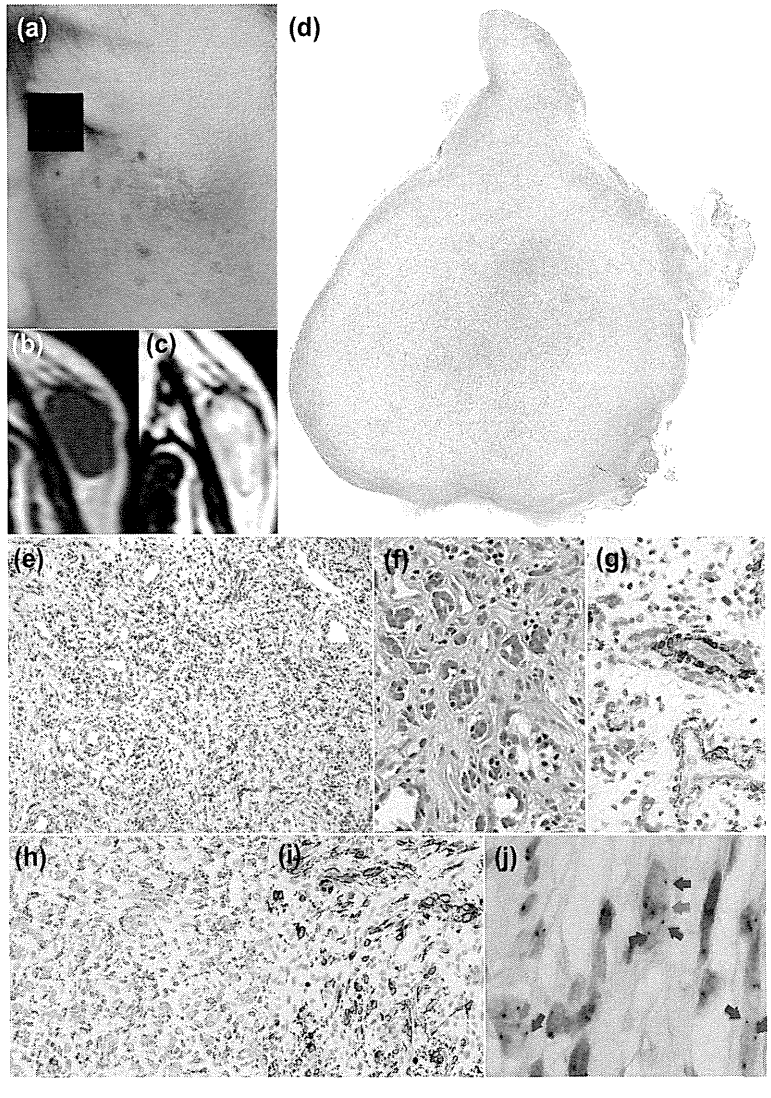

Fig. 1. (a) Clinical features of angiofibroma of soft tissue (AFST) on the patient's face at her initial visit to us. There is a surgical scar on the tumour. (b) Magnetic resonance imaging (MRI) T1, (c) MRI T2; in MRI images, the patient has a well-defined mass on the left cheek. The size is 8 × 10 mm. T1- and T2-weighted MRI images illustrate the tumour as having hypointense and hyperintense signals, respectively. This imaging pattern is indicative of an inflammatory lesion or a benign tumour. (d) Histopathologically, the tumour is sharply demarcated with no apparent capsule (haematoxylin and eosin (HE) staining, original × 12.5). (e) The proliferation of spindle cells, small vessels and the infiltration of lymphocytes are seen in the tumour (HE staining, original × 40). (f) Giant cells are also observed in the tumour (HE staining, original × 200). Immunohistochemically, the tumour cells are (g) weakly positive for α-smooth muscle actin (α-SMA) and (h) positive for CD68 and (i) desmin (original × 200, respectively). (j) Chromogenic *in situ* hybridization (CISH) for detection of nuclear receptor coactivator 2 gene (*NCOA2*) rearrangement (original × 1,000). Unpaired signals (*red and blue arrows*), representing *NCOA2* disruption, are observed in some tumour cells.

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DISCUSSION

To date, approximately 40 cases of AFST have been reported worldwide. AFST tends to grow slowly. In the literature, we found one case that had been followed up for more than 10 years before resection (1). AFST may be misdiagnosed as low-grade sarcoma (1). In fact, Marino-Enriquez & Fletcher (1) reported that 4 out of 28 AFST cases developed local recurrence, even though a positive surgical margin was detected at the initial resection in only one of the 4 patients with recurrence. Metastasis of AFST has never been reported (1). The most common sites of AFST are the limbs, particularly the lower extremities (1). To our knowledge, this is the first reported case of AFST on the face. AFST on the limbs is usually not tender; only 2 patients out of the 29 reported AFST cases on the limbs (6.9 %) reported feeling tenderness (1). In contrast, the present patient had tenderness on the AFST lesion on their face.

To confirm the diagnosis of AFST, we performed CISH for detection of gene rearrangement of *NCOA2* and obtained positive results. It was reported that 7 out of 14 cases of AFST were positive for *NCOA2* gene rearrangement (3). This is because NCOA2-rearranged cells can be infrequent and only found in limited numbers of tumour cells. In such a tumour, CISH is a useful adjunct, which enables sensitive analysis of tumour cells and which is superior to reverse transcription polymerase chain reaction (RT-PCR) and fluorescence *in situ* hybridization (FISH) (5).

In conclusion, the present case clearly indicates that AFST can occur on the face and suggests that CISH for *NCOA2* gene rearrangement is a powerful diagnostic tool for AFST, especially for AFST lesions on unusual body sites. To avoid overtreatment, we propose that it is important to make a precise diagnosis of AFST and to distinguish it from more aggressive tumours of the soft tissues.

The authors declare no conflicts of interest.

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■衛生・公衆衛生学

「人を対象とする医学系研究に関する倫理指針」への統合

2015年4月より，これまでの「疫学研究に関する倫理指針」，「臨床研究に関する倫理指針」が統合され，「人を対象とする医学系研究に関する倫理指針」[1]に基づいて行うことが求められている。

主な変更点では，「侵襲」がかなり明確に定義された。「精神的侵襲」への言及がなされ，「研究目的に造影剤を使うMRIを施行」も侵襲と定義された。インフォームド・コンセントを受ける能力を欠くと客観的に判断される研究対象者（小児など）に対し，その理解力に応じたわかりやすい言葉で説明をするインフォームド・アセントも規定されている。近年のデータの信頼性に問題のあった大規模臨床試験の事例の影響と考えられる特に注目すべき点は，侵襲のある介入研究にモニタリング（研究者によるデータなどの定期的な確認）が義務化され，必要に応じて監査（信頼性確保のための研究から独立したものによる調査）を行うことが求められるようになったことである（施行は2015年10月から）。

そのほか，改めて利益相反を正しく開示して，研究計画書に記載し対象者へ説明することや，介入研究はデータベース登録が求められていることはこれまで通りである。なお，研究目的でない純粋に患者への医療として行う場合は本倫理指針の適用外となるが，保険適用外の治療などでエビデンスが不十分な場合には，客観的な立場の倫理審査を受けて行うなどの配慮が必要と考える。また，再生医療新法により，自由診療においても法律で定義される再生医療はすべて審査が必要となる。

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【解説】

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■皮膚科

次世代シークエンスにより明らかになってきた色素異常症の原因

色素異常症には，日本人が初めて報告し，現在でも報告者の名前で呼ばれている疾患がある。それは，色素斑と脱色素斑が混在した皮疹が四肢末端に出現する遺伝性対側性色素異常症（遠山），遺伝性対側性色素異常症の色素斑が全身に広がる遺伝性汎発性色素異常症（市川-平賀），そして，四肢末端に網目状の色素斑を認める網状肢端色素沈着症（北村）の3疾患である。

遺伝性対側性色素異常症の病因は，2003年に二重鎖RNA編集酵素をコードするADAR1の遺伝子変異であることが明らかになっていたが[1]，ほかの2疾患については，疾患概念の提唱以来数十年間，病因は不明であった。しかし2013年，次世代シークエンスという新しい遺伝子解析技術を用いることにより，網状肢端色素沈着症は蛋白の細胞外ドメインを切断する酵素ADAM10[2]の，また，遺伝性汎発性色素異常症は膜輸送や糖化に関与するABCB6[3]の遺伝子変異が原因であることがわかった。

様々な色素異常症の原因遺伝子が次々と明らかになったことで，今後，皮膚の色に関する調整機構の全体像の解明が期待される。

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【解説】

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特集 ここまで変わった！ 子どものアレルギー診療

Column アトピー性皮膚炎とフィラグリン遺伝子

皮膚のバリアシステム形成におけるフィラグリンの役割と，フィラグリン遺伝子変異のアトピー性皮膚炎発症への関与について解説します。

名古屋大学大学院医学系研究科皮膚病態学分野（皮膚科学）
河野通浩（こうのみちひろ），秋山真志（あきやまましし）

はじめに ～フィラグリンとは～

アトピー性皮膚炎（atopic dermatitis：AD）はいくつかの要因が関係している疾患ですが，近年，皮膚のバリア異常が病態に関係していることが明らかになっています。

皮膚のバリア機能によって，体表面からの水分蒸散量はコントロールされ，外界からのアレルゲンなどの異物の侵入も防がれています。

この皮膚のバリア機能は，皮膚の最上層にある，わずか0.02 mmの角質層が大きな役割を果たしています。そして，その維持において中心的な役割をしているたんぱくのひとつがフィラグリンです。

フィラグリンは皮膚の角化細胞内で産生されたプロフィラグリンが10～12個に切断されてできる分子で，ケラチンとともに角化細胞内を満たします。この過程は正常の角化に非常に重要です。

尋常性魚鱗癬の原因としてのフィラグリン遺伝子変異

そのプロフィラグリンをコードするフィラグリン遺伝子（*FLG*）は，2006年にヨーロッパの尋常性魚鱗癬家系において遺伝子変異が明らかになり[1]，当初は尋常性魚鱗癬の原因遺伝子として脚光を浴びました。

尋常性魚鱗癬は，四肢伸側の軽症から中等症までの過角化（いわゆるさめ肌）がおもな症状で，最も頻度の高い遺伝性皮膚疾患の1つです。ヨーロッパ人の4%弱が*FLG*変異を有していることが明らかになり[1]，その後，ヨーロッパ人には，少なくとも13個の*FLG*変異が同定されています[2]。

日本人の尋常性魚鱗癬患者家系において，ヨーロッパから報告のあった*FLG*変異の有無をスクリーニングしたところ，興味深いことに，同じ変異は認められず[3]，7つの日本人固有の新規遺伝子変異が同定されました[3~6]。

現在までに日本人では10個の変異が明らかになっていますが[7]，1つの例外[8]を除いて，日本人はヨーロッパ人とまったく異なる固有の*FLG*変異を有していることが明らかになりました。

アトピー性皮膚炎の重要な発症因子としてのフィラグリン遺伝子変異

ADには多様な病因・増悪因子が関与し，また，各症例によってそれらはさまざまであると推測されていますが，以前より尋常性魚鱗癬患者

著者プロフィール　河野通浩　1999年秋田大学大学院医学系研究科修了。愛知医科大学皮膚科，マサチューセッツ総合病院病理部門留学を経て，現在，名古屋大学大学院医学系研究科皮膚病態学分野講師。皮膚の遺伝病，特に色素異常症とアトピー性皮膚炎の研究に取り組んでいる。

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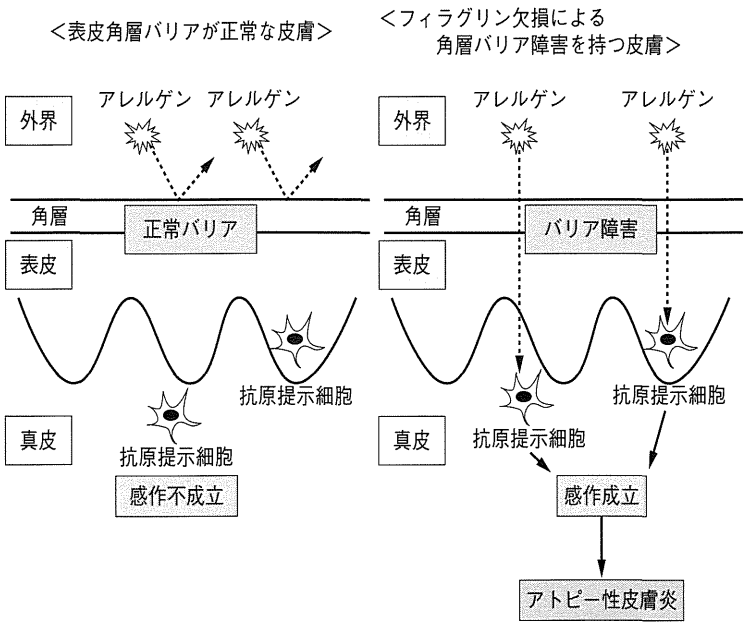

図1 フィラグリン遺伝子変異がアトピー性皮膚炎発症因子となる機序
角層のバリア障害により，外部環境からのアレルゲンの侵入が容易になり，感作が成立して，アトピー性皮膚炎が惹起されると考えられている。
〔秋山真志：フィラグリン遺伝子変異とアトピー性皮膚炎．日本医師会雑誌 138：2536-2537，2010 より一部改変〕

にADの合併がみられることが知られていました。

2006年*FLG*が尋常性魚鱗癬の原因遺伝子であることが明らかになった直後に，ADと*FLG*の関連を調べる研究の結果が報告され，アイルランド人では*FLG*変異がADの約半数でみられることが明らかになりました[9]。その後のおもにヨーロッパ人で施行された研究のメタアナリシスにおいてAD患者の21.6%が*FLG*変異を有していると報告され[10]，*FLG*変異により引き起こされる皮膚バリア機能異常がAD発症と深く関係していることは，もはや疑いのない事実として認知されました[11]。

日本人についても，前述した7つの日本人固有の*FLG*変異について，日本人AD患者を対象としたスクリーニングを行いました[3~6]。その結果，これらの*FLG*変異はAD患者群では27%以上にみられ，日本人では，これらの日本人固有の*FLG*変異がADの重要な発症因子であることが示されました[6]。すなわち，日本人AD患者の3割弱は，フィラグリンの遺伝子変異を発症因子として有しているわけであり，ADの病因を考える際に，非常に重要な要因だといえます。

さて，*FLG*変異がADを引き起こすメカニズムとしては，**図1**のように，フィラグリン減少に起因する皮膚バリア障害が，ダニなどのアレルゲンの侵入を容易にして，その結果，感作によるIgE高値と皮膚炎を引き起こす，ということが考えられています[12,13]。

さらに近年では，*FLG*変異がAD以外の気管支喘息やアレルギー性鼻炎，食物アレルギーのリスク因子になることが徐々に明らかになってきており，アトピー性疾患全般とフィラグリンの関連に注目が集まっています。

フィラグリン遺伝子変異に基づくテーラーメイド医療と迅速変異検出法

私たちは*FLG*変異検索に基づく，アトピー疾患のテーラーメイド医療を提案しています。*FLG*変異を有する患者は皮膚バリア機能障害が病因であると考えられるため，バリア障害を改善するための治療をするという根本的な治療が可能になると考えています。さらに，*FLG*変異を有する小児に対しては積極的に保湿薬などの皮膚バリア機能を補う外用を行い，ダニなどの曝露を減らすなどの方法によるADの発症予防も可能になると考えています。

今後は大量の検体を処理する必要があるため，リアルタイムPCR[*1]によるdouble dye probe[*1]を用いた日本人の既出*FLG*変異を検出する手法を確立しました。本法により，大量検体を迅速安価に解析することがで

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[*1]リアルタイムPCR，double dye probe：リアルタイムPCRとは，DNAの定量を行うPCR法のひとつ。double dye probeという両側に蛍光がついたプローブを用いて，PCR反応を経時的（リアルタイム）に測定する。遺伝子変異・多型の検出にも用いられている。

きるようになりました。この手法を用いて，820人の検診受検者の*FLG*変異解析を行い，*FLG*変異とアレルギー性鼻炎の関連性を明らかにし，実用性を証明しました[14]。

今後は，この手法を使って大規模遺伝子解析を行い，さらに日本人における*FLG*変異とアレルギー疾患に関する関連性を明らかにするとともに，テーラーメイド治療・予防法の確立を進めたいと思います。

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The dyschromatoses

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INTRODUCTION — The dyschromatoses are a group of rare, inherited pigmentary disorders characterized by the development during infancy or childhood of numerous, irregular hyperpigmented and hypopigmented macules approximately 5 mm in diameter [1]. Dyschromatosis symmetrica hereditaria (DSH, MIM #127400) and dyschromatosis universalis hereditaria (DUH, DUH1 MIM #127500, DUH2 MIM #612715, DUH3 MIM #615402), which are the two most common dyschromatoses, were first reported and most commonly occur in Japan.

This topic will discuss the clinical manifestations, diagnosis, and treatment of DSH and DUH. Other congenital and inherited hyperpigmentation disorders and the acquired hyperpigmentation disorders are discussed separately. (See "Approach to the patient with hyperpigmentation disorders".)

EPIDEMIOLOGY — Epidemiologic data on the inherited dyschromatoses are limited. The prevalence of dyschromatosis symmetrica hereditaria (DSH) in Japan is estimated to be approximately 1.5 per 100,000 [2]. The prevalence of dyschromatosis universalis hereditaria (DUH) is probably much lower than DSH prevalence. One study reported that approximately 1.9 and 0.3 per 100,000 dermatology consultations in Japan are related to DSH and DUH, respectively [3].

DYSCHROMATOSIS SYMMETRICA HEREDITARIA — Dyschromatosis symmetrica hereditaria (DSH), also called reticulate acropigmentation of Dohi, is an autosomal dominant disorder characterized by a mixture of hypopigmented and hyperpigmented macules approximately 5 mm in diameter on the dorsa of the hands and feet (picture 1) and freckle-like macules on the face. First described by Toyama in 1910, DSH has been reported mainly in Japan and China [4,5]. However, Korean [6], Taiwanese [7], Thai [8], Indian [9], Turkish [10], European [11,12], and Hispanic [13] cases have also been reported.

Genetics — DSH (MIM#127400) is caused by mutations in the adenosine deaminase acting on RNA1 gene (*ADAR1*) at 1q21.3, which encodes the RNA editing enzyme [2]. DSH is inherited in an autosomal dominant manner with nearly complete penetrance but variable expressivity. Both familial and sporadic cases have been reported. More than 130 different mutations throughout *ADAR1* have been described in patients with DSH. These mutations, including nonsense, missense, frameshift, and splice-site mutations, are thought to lead to *ADAR1* haploinsufficiency.

Pathogenesis — Adenosine deaminase acting on RNA1 (ADAR1) is an RNA-editing enzyme that catalyzes the deamination of adenosine to inosine in double-stranded RNA substrates during post-transcription processing [14]. Inosine acts as guanine during translation, resulting in codon alterations or alternative splicing sites that lead to functional changes in proteins [15].

ADAR1 has two isoforms of different sizes, regulated by different promoters: constitutively expressed ADAR1-p110 (110 kDa) and interferon-inducible ADAR1-p150 (150 kDa) [16]. Regulated by different promoters, the two variants are thought to be involved in different cellular functions, including stem cell maintenance, protection against stress-induced apoptosis, and innate immune response [17-20]. Studies indicate that the interferon-inducible ADAR1-p150 promoter is involved in the modulation of the response to several viral infections, including measles, influenza, hepatitis C, hepatitis D, lymphocytic choriomeningitis, and polyoma virus infection [21,22].

Mutation analysis has shown mutations in the coding region only of the p150 isoform in DSH patients [23]. This finding supports the hypothesis that DSH is caused by the p150 isoform of *ADAR1*, although the

substrate gene edited by ADAR1 in the skin is unknown. Further studies are needed to clarify the mechanisms underlying the degeneration and/or dysfunction of melanocytes in DSH and its localization to the distal extremities and face, despite the ubiquitous expression of *ADAR1* [17,24].

Clinical features — DSH is characterized by a mixture of hypopigmented and hyperpigmented macules approximately 5 mm in diameter, distributed predominantly on the dorsal aspect of the hands and feet (picture 1), but sometimes extending to the dorsal aspect of the extremities (picture 2). In some patients, freckle-like macules develop on the face (picture 3). Palms, soles, and mucosa are uninvolved.

DSH commonly develops during infancy or early childhood [25]. Lesions first appear before the age of six years in approximately 70 percent of cases [26]. Lesions extend progressively during childhood, become stable before adolescence, and then persist for life [25,27]. Skin findings are more pronounced after sun exposure, although patients do not show photosensitivity [26,28,29].

Lesions are asymptomatic and do not show telangiectasia, atrophy, or scale. Inter- and intrafamilial phenotypical variation has been reported [30]. It is the author's experience that some parents may have only faint hypopigmented macules on the dorsa of the fingers, whereas their children have widespread macules over the extremities.

DSH is, in most cases, an isolated disorder. However, there are rare reports of DSH in association with other disorders, including neurologic disorders [27,31], psoriasis [32], acral hypertrophy [33], and depression [34].

Histopathology — Histopathologic examination of lesional skin shows little melanin in hypopigmented macules and increased melanin pigmentation in the basal layer of hyperpigmented lesions along with pigmentary incontinence [7,30]. In the hypomelanotic areas, as well as in the surrounding normal skin, there is a decreased number of melanocytes; in the hyperchromic areas, melanocytes appear increased in size, with elongated and numerous dendrites, indicating active melanosome transfer to the keratinocytes [7]. Electron microscopy studies have shown abnormalities in melanocytes in the hypomelanotic skin, including a decrease in number, fatty degeneration, vacuolization of cytoplasm, swollen mitochondria, and condensed, irregularly shaped nucleus [7,30].

DYSCHROMATOSIS UNIVERSALIS HEREDITARIA — Dyschromatosis universalis hereditaria (DUH) is a rare pigmentary genodermatosis characterized by hypopigmented and hyperpigmented macules involving the entire body surface. First described in 1933 by Ichikawa and Hiraga [35], it occurs predominantly in the Japanese [36,37] but has also been reported in other Asian [38,39], Middle Eastern [40,41], European [36], South American, and African populations [42-44].

Genetics — DUH shows genetic heterogeneity. It is inherited in an autosomal dominant fashion with variable penetrance, but there are reports of autosomal recessive transmission [40,45]. Sporadic cases have also been described [46].

In two Chinese families, the locus for the autosomal dominant form (DUH1, MIM #127500) was mapped at chromosome 6q24-q25.2 [47]. In another pedigree, the locus for the autosomal recessive form, DUH2 (MIM #612715), was mapped at chromosome 12q21-q23 [45]. However, the pathogenic genes of these subtypes have not been identified [45,47].

Subsequent genome-wide linkage analysis studies in two large Chinese kindreds with multiple members affected over five generations indicated that DUH (DUH3, MIM #615402) is caused by mutations in the adenosine triphosphate (ATP)-binding cassette subfamily B, member 6 gene (*ABCB6*) at 2q35, encoding a transporter protein that regulates de novo porphyrin synthesis [48,49].

Pathogenesis — DUH is thought to be caused by a deficiency of melanin synthesis and/or melanosome sorting [36,50,51]. The *ABCB6* gene is widely expressed in many tissues. In the skin, the ABCB6 protein is expressed in keratinocytes and melanocytes and has a diffuse cytoplasmic distribution, including the outer mitochondrial membrane, endoplasmic reticulum, Golgi apparatus, plasma membrane, and exosomes [48].

In a study of mouse melanoma B16 cell line, the wild-type ABCB6 protein was distributed in an

endosome-like pattern and was abundant in the dendrites, whereas the ABCB6 protein with the mutations found in DUH was retained in the Golgi body [48]. These preliminary findings suggest that ABCB6 may be involved in the transfer of melanosome to keratinocytes.

Histopathology — Histologic examination of a skin biopsy shows, in DUH, a focal increase or decrease in the melanin content of the basal layer in hyper- and hypopigmented macules, respectively. Pigment incontinence is occasionally observed. An ultrastructural study demonstrated normal numbers of active melanocytes but different amounts of fully melanized melanosomes in hyperpigmented and hypopigmented macules [36].

Clinical features — DUH usually presents in the first year of life with asymptomatic hyperpigmented and hypopigmented irregular macules similar to those seen in DSH, located mainly on the trunk (picture 4) but also on the face and extremities [1]. Lesions on the face may resemble ephelides or lentigines. The palms, soles, and mucosal surfaces are usually spared but may be involved [38,52].

DUH usually occurs in isolation. However, there are reports of DUH associated with systemic complications, including short stature, deafness, epilepsy, and erythrocyte, platelet, and tryptophan metabolism abnormalities [1,38,39,53].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS — The diagnosis of inherited dyschromatosis is usually clinical. Histology is nonspecific and shows focal increase or decrease in melanin content of the basal layer in the hyperpigmented and hypopigmented macules, respectively.

Although the individual macular lesions of dyschromatosis symmetrica hereditaria (DSH) and dyschromatosis universalis hereditaria (DUH) are indistinguishable on typical cases, differentiating DSH from DUH is usually not difficult based upon clinical findings, including lesion distribution and time of onset. In DSH, lesions manifest during childhood and are typically limited to the distal extremities, whereas, in DUH, lesions appear in the first year of life on the trunk and then extend to the entire body surface.

Genetic testing is not routinely performed; however, it may be helpful in difficult cases to differentiate DSH and DUH from each other and from other inherited disorders of pigmentation. Inherited and acquired pigmentary disorders that may be confused with DSH or DUH include:

- **Reticulate acropigmentation of Kitamura** – Reticulate acropigmentation of Kitamura (RAK, MIM #615537) is a rare genodermatosis caused by mutations in the *ADAM10* gene, encoding A disintegrin and metalloproteinase domain-containing protein 10 [54]. RAK is characterized by dot-like or reticulate, slightly depressed, sharply demarcated, hyperpigmented macules affecting the dorsa of the hands (picture 5) and feet and palmoplantar pits [55]. In contrast to DSH, hypopigmented macules are absent in RAK. (See "Approach to the patient with hyperpigmentation disorders", section on 'Reticulate acropigmentation of Kitamura'.)

- **Xeroderma pigmentosum** – Xeroderma pigmentosum (XP) is a rare autosomal recessive disease caused by mutations in genes involved in nucleotide excision repair of carcinogen adducts induced by ultraviolet (UV) irradiation [56]. XP is characterized by extreme sensitivity of the skin to sunlight, abnormal pigmentation, xerosis, telangiectasia, atrophy, and a high tendency to develop skin cancers at a very early age. Mild cases of XP or the early stage of XP in a child may be sometimes difficult to differentiate from XP [29]. Photosensitivity tests, cellular hypersensitivity to UV radiation, complementation studies and chromosomal breakage studies using the patient's fibroblasts, and genetic analyses can be performed for definite diagnosis [29]. (See "The genodermatoses", section on 'Xeroderma pigmentosum'.)

- **Amyloidosis cutis dyschromica** – Amyloidosis cutis dyschromica is an exceedingly rare type of primary cutaneous amyloidosis characterized by reticular hyperpigmentation with hypopigmented macules distributed over nearly all of the body (picture 6). Histologic examination of a skin biopsy shows hyperkeratosis, necrotic keratinocytes in the basal layer, and melanophages as well as amorphous eosinophilic material (amyloid) deposits in the upper dermis. (See "Approach to the patient with hyperpigmentation disorders", section on 'Primary cutaneous amyloidosis'.)

Exposure to chemicals that are toxic to melanocytes, such as diphenylcyclopropenone and monobenzyl ether of hydroquinone, may cause patchy depigmentation that may mimic the dyschromatoses [57]. History of exposure to these agents usually clarifies the diagnosis. Histologic examination of a skin biopsy shows absence of melanocytes in the hypopigmented areas.

TREATMENT — There are no effective treatments for the hereditary dyschromatoses. Because tanning emphasizes the contrast between hyperpigmented and hypopigmented spots, patients with dyschromatosis should adopt photoprotection measures, including sun avoidance and use of protective clothing and broad-spectrum sunscreens with a sun protection factor (SPF) of at least 30.

There is a single case report of treatment of DSH lesions using miniature punch grafting followed by excimer light therapy [58]. The Q-switched alexandrite laser has been successfully used to remove facial and labial lentigines in a single patient with DUH [59].

SUMMARY AND RECOMMENDATIONS

- The dyschromatoses are a group of rare inherited pigmentary disorders mainly reported in Japan and China and characterized by the presence of numerous irregular hyperpigmented and hypopigmented macules approximately 5 mm in diameter. (See 'Introduction' above.)

- Dyschromatosis symmetrica hereditaria (DSH), also called reticulate acropigmentation of Dohi, is an autosomal dominant disorder caused by mutations in *ADAR1* gene, encoding the RNA editing enzyme adenosine deaminases acting on RNA1 (ADAR1). DSH develops during infancy or early childhood and is characterized by a mixture of hypopigmented and hyperpigmented macules approximately 5 mm in diameter on the dorsa of the hands and feet and freckle-like macules on the face (picture 7A-B). (See 'Dyschromatosis symmetrica hereditaria' above.)

- Dyschromatosis universalis hereditaria (DUH) is a rare pigmentary genodermatosis characterized by hypopigmented and hyperpigmented macules, which is the same as the lesion of DSH, involving the entire body surface (picture 4). DUH is inherited in an autosomal dominant or recessive manner and shows genetic heterogeneity. DUH has been reported in association with short stature, deafness, epilepsy, and erythrocyte, platelet, and tryptophan metabolism abnormalities. (See 'Dyschromatosis universalis hereditaria' above.)

- The diagnosis of inherited dyschromatosis is usually clinical. Histology is nonspecific and shows focal increase or decrease in melanin content of the basal layer. Genetic testing is not routinely performed; however, it may be helpful in difficult cases to differentiate DSH and DUH from each other and from other inherited or acquired disorders presenting with dyspigmentation, such as reticulate acropigmentation of Kitamura (RAK), xeroderma pigmentosum (XP), and amyloidosis cutis dyschromica. (See 'Diagnosis and differential diagnosis' above.)

- There are no effective treatments for the inherited dyschromatoses. Photoprotection measures, including sun avoidance and use of protective clothing and broad-spectrum sunscreens with a sun protection factor (SPF) of at least 30 may be helpful to avoid contrast enhancement between hyperpigmented and hypopigmented macules. (See 'Treatment' above.)

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