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*http://www.uptodate.com/contents/the-dyschromatoses

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Received 28 May 2015
Received in revised form 24 June 2015
Accepted 1 July 2015

http://dx.doi.org/10.1016/j.jdermsci.2015.07.001

Letter to the Editor

Impetigo herpetiformis with *IL36RN* mutations in a Chinese patient: A founder haplotype of c.115+6T>C in East Asia

Keywords:
Founder haplotype
Generalized pustular psoriasis
IL36RN
Impetigo herpetiformis
Interleukin-36 receptor antagonist

Impetigo herpetiformis (IH) is a rare pustular dermatosis of pregnancy [1]. Most patients with IH do not have personal and family histories of psoriasis. Early diagnosis is essential, as IH occasionally leads to maternal or foetal death. Despite the clinical importance of IH, its aetiology has not been clarified sufficiently. Recently, we reported two Japanese cases of IH with homozygous and heterozygous mutations of *IL36RN*, which encodes the interleukin-36 receptor antagonist (IL-36RN) [2]. However, the incidence of IH cases with *IL36RN* mutations is unknown. To our knowledge, no subsequent case of IH with or without an *IL36RN* mutation has been reported thus far.

After a long-standing controversy over whether IH is an independent disease entity from generalized pustular psoriasis (GPP), today there is a tentative consensus that IH is GPP occurring during pregnancy [3]. We reported that most GPP cases that are not accompanied by psoriasis vulgaris (PV; GPP alone) are caused by *IL36RN* mutations, although only a small number of cases with GPP preceding or accompanied by PV were found to have *IL36RN* mutations [4].

Here, we report a case of IH in a Chinese patient with a homozygous *IL36RN* mutation c.115+6T>C, the most frequent GPP-causing mutation in the Chinese population. We also found a novel haplotype of *IL36RN* c.115+6T>C, which is a probable founder haplotype, both in the present patient and in 2 Japanese families.

The patient was a 25-year-old Chinese woman who was admitted to our hospital for pustular lesions after her first normal vaginal delivery (Fig. 1a). She had neither a family history of GPP and IH nor consanguinity in her family. She had no history of GPP. Her pustular lesions began to develop at the 29th week of her first pregnancy, and she had been treated in a maternity hospital. Oral betamethasone of 3 mg/day was administrated, although the eruptions persisted. The skin biopsy of a specimen from a pustular eruption on the trunk revealed a spongiform pustule of Kogoj in the epidermis, consistent with IH (Fig. 1b). She had erythema with pustules all over her body and fever of a body temperature higher than 38 °C. Blood examinations revealed white blood cell counts of 31,590/μL and C-reactive protein concentrations of 2.45 mg/dL (reference range: <0.3 mg/dL). Bacterial culture of the pustules yielded negative results. Thus, she was diagnosed as having IH.

After ethical approval, informed consent was obtained in compliance with the guidelines of the Declaration of Helsinki. The entire coding regions of *IL36RN*, including the exon/intron boundaries, were sequenced by using a genomic DNA sample from the patient. The patient had the homozygous mutation c.115+6T>C (p.Arg10ArgfsX1), which is a GPP-causing mutation that was found in both Chinese and Japanese cohorts [4–6] (Fig. 1c).

We previously reported *IL36RN* c.115+6T>C as a founder mutation (haplotype; ACTACACC) in a Japanese GPP cohort [4]. Later, in Japanese GPP and IH cases [2,7], we found another haplotype (ACCGAGCC) of c.115+6T>C and herein report the haplotype for the first time. The analysis method for the haplotype of *IL36RN* was described previously [4]. The present Chinese patient also had the haplotype (ACCGAGCC). Thus, the haplotype seems to be shared by the Chinese and Japanese populations.

The prevalence of the *IL36RN* mutation c.115+6T>C is 0.90% (10/1,114 individuals) in the Japanese population and 4.1% (15/365 individuals) in the Chinese population [6,8]. However, the prevalence of the *IL36RN* mutation c.115+6T>C of the specific haplotype (haplotype: ACCGAGCC) in both populations is not known. The *IL36RN* mutation c.115+6T>C (haplotype: ACTACACC) has not been reported in the Chinese population. However, independent from the haplotype, it might be an IH-causing mutation in the Chinese population.

Several twin or sibling cases of IH have been reported [9,10]. Therefore, IH has been thought to be a genetic disease, although the genetic background had been unknown. To date, we have sequenced *IL36RN* in 3 IH cases, including the present case, and found that all of the 3 cases had *IL36RN* mutations [2]. Only a small number of IH patients have been studied genetically, including the present case; thus, further studies of a large number of IH patients are needed in the future.

Abbreviations: GPP, Generalized pustular psoriasis; IH, Impetigo herpetiformis; IL-36, RNInterleukin-36 receptor antagonist; PV, psoriasis vulgaris.

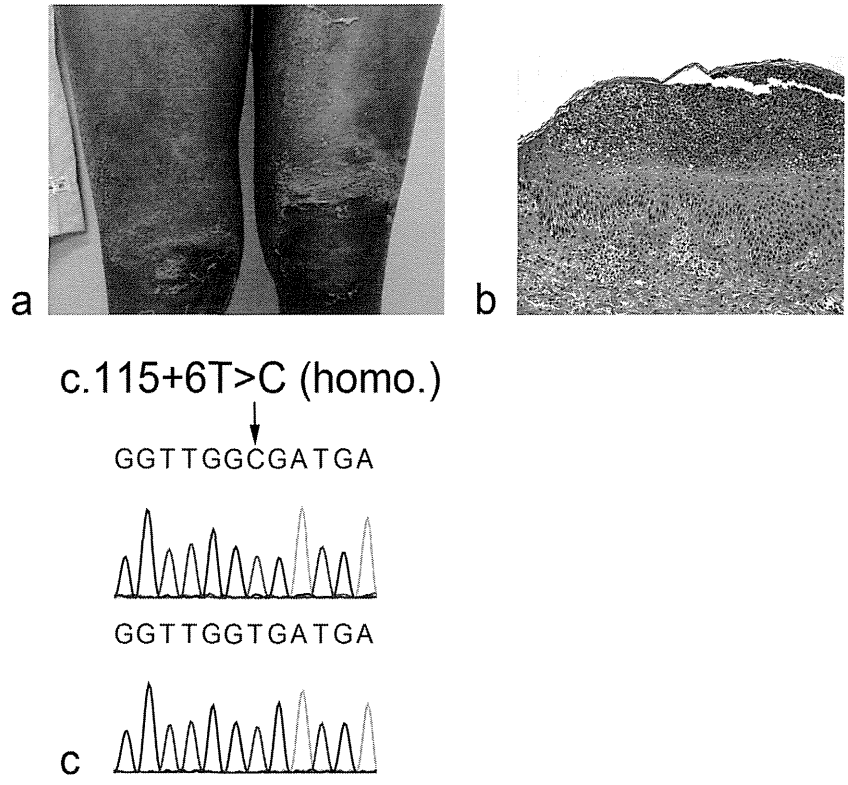

Fig. 1. Clinical and histopathologic features, and mutation analysis of *IL36RN* in the patient
The clinical features of the present case (a). Pustules on the background erythema are seen on the thighs. The pathologic features of the pustules (b). Spongiosis of Kogoj and acanthosis can be seen in the epidermis of the pustular erythematous lesions on the trunk (original magnification: × 200). Direct sequencing reveals the homozygous mutation c.115+6T>C in the present case (c).

In conclusion, the present case further support that IH and GPP, especially GPP alone, are identical diseases caused by *IL36RN* mutations.

Conflicts of interests

The authors have no conflicts of interests to declare.

Acknowledgements

The authors thank Ms. Haruka Ozeki and Ms. Yuka Terashita for their technical help in analysing *IL36RN* mutations. This study was supported in part by a Grant-in-Aid for Scientific Research (B) to K.S. (15H04886), a Grant-in-Aid for Challenging Exploratory Research to K.S. (15K15414), a Grant-in-Aid for Scientific Research (B) to M.A. (15H04887), and a Grant-in-Aid for Challenging Exploratory Research to M.A. (15K15415), from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and by the grant H26-itaku (nan)-ippan-027 to K.S. from the Ministry of Health, Labour and Welfare (Research on Measures for Intractable Disease), Japan.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2015.06.003.

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Received 4 March 2015
Received in revised form 3 June 2015
Accepted 5 June 2015

http://dx.doi.org/10.1016/j.jdermsci.2015.06.003

Journal of Dermatological Science xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Letter to the Editor

Porokeratotic eccrine ostial and dermal duct nevus with a somatic homozygous or monoallelic variant of connexin 26

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) is an uncommon, benign dermatosis characterized by asymptomatic keratotic papules and plaques with a linear distribution mainly on the extremities. Histopathologically, PEODDN is characterized by the presence of a cornoid lamella exclusively overlying eccrine acrosyringia or overlying both eccrine acrosyringia and hair follicles. The lesions usually appear at birth or in childhood [1] and are localized at the extremity of a single limb, although wider distribution has occasionally been documented. The molecular cause of PEODDN has not been completely clarified. Recently, somatic mutations in the gene (*GJB2*) encoding the gap junction protein connexion 26 (Cx26) were presented to be a cause of PEODDN [2,3]. Here, we report a patient with PEODDN in whom a somatic homozygous or monoallelic variant of Cx26 was confirmed in the lesional skin.

A 10-year-old male presented to our hospital with unilateral dominant linear skin lesions. He was the son of healthy, nonconsanguineous parents, and was born at full term after an uneventful pregnancy. He was generally in good health, and had achieved normal development. His familial history was negative for similar cutaneous disorders. His parents first recognized a change in skin colour on his right armpit at the age of 2. The skin lesions began to spread to his right upper arm and forearm when he was 5 years old. He was treated at another hospital with topical steroids, but the condition did not resolve.

Upon first visiting our hospital, the dermatosis consisted of hyperkeratotic streaks with bilateral, asymmetrical distribution following Blaschko's lines (Fig. 1a–c). Physical examination revealed red-coloured macules and white hyperkeratotic papules, localized to the right side of the body involving the fifth finger, forearm, upper arm, armpit, thigh, lower leg, and popliteal fossa, strictly respecting the midline.

Histopathology from a representative skin lesion showed hyperkeratosis, acanthosis, and papillomatosis under low power magnification. Keratotic invaginations with prominent parakeratosis overlying a hair follicle were observed. The granular layer was absent below the parakeratotic column (Fig. 1d). These histopathologic features are characteristic of PEODDN.

Following ethical approval, informed written consent was obtained from the patient in compliance with the Declaration of Helsinki guidelines. The coding regions of *GJB2*, including the exon–intron boundaries, were amplified by PCR from genomic DNA obtained from the lesional epidermis and peripheral blood of the patient as described elsewhere [4]. Later, the exon 1 and intron 1–2 of *GJB2* were also amplified by PCR from genomic DNA obtained from the peripheral blood of the patient. The mutation analysis of *GJB2* revealed that the patient's blood was heterozygous for the missense variant c.608T>C (p.Iso203Thr), and was homozygous or monoallelic for the variant in the lesional epidermis (Fig. 2). No other heterozygous *GJB2* variant was found in the patient's blood. According to the 1000 genomes project (http://www.1000genomes.org/), 9 out of 89 Japanese subjects had the heterozygous variant p.Iso203Thr, but none was homozygous for the variant. The Sorting Intolerant from Tolerant (SIFT) score (http://sift.jcvi.org/) of the variant was 0.000, which predicted that p.Iso203Thr is deleterious. The PolyPhen-2 score (http://genetics.bwh.harvard.edu/pph2/) was 0.541, which indicated that the variant has possibly damaging effects.

It is currently thought that PEODDN is a mosaic form of keratitis-ichthyosis-deafness (KID) syndrome caused by a mutation in *GJB2* [2,3]. By using whole-exome sequencing, Levinsohn et al. showed that somatic GJB2 mutation alone is sufficient to cause PEODDN [3]. In Easton et al. and Levinsohn et al. causative *GJB2* mutations appeared to induce a protein gain-of-function [2,3]. Heterozygous mutations caused aberrant opening of gap junctions in epidermal keratinocytes, resulting in PEODDN. The *GJB2* mutation/variant in the present case seems to not be pathogenic when heterozygous since, according to the 1000 genomes project, heterozygous p.Iso203Thr Cx26 was found in 32 individuals without KID syndrome out of 286 individuals, exclusively in Asian (Chinese and Japanese) populations. No homozygous p.Iso203Thr Cx26 individuals were reported, suggesting that homozygous p.Iso203Thr Cx26 may be pathogenic and possibly lethal in humans. Both the SIFT score and the PolyPhen-2 score predicted the variant to be deleterious or damaging. We therefore consider the present case of epidermal somatic homozygous or monoallelic variant of Cx26 as a possible cause of PEODDN. The present patient is heterozygous for the variant p.Iso203Thr, but keratinocytes within the lesional epidermis are homozygous or monoallelic for the *GJB2* variant. Hence, we believe *GJB2* mutations and variants can induce PEODDN.

In conclusion, we show for the first time, to our knowledge, a somatic homozygous or monoallelic variant of Cx26 in the lesional epidermis of PEODDN. This finding supports the theory that somatic *GJB2* mutations cause PEODDN [2,3].

Abbreviation: Cx26, connexion 26; KID, keratitis-ichthyosis-deafness; PEODDN, porokeratotic eccrine ostial and dermal duct nevus.

http://dx.doi.org/10.1016/j.jdermsci.2015.07.003

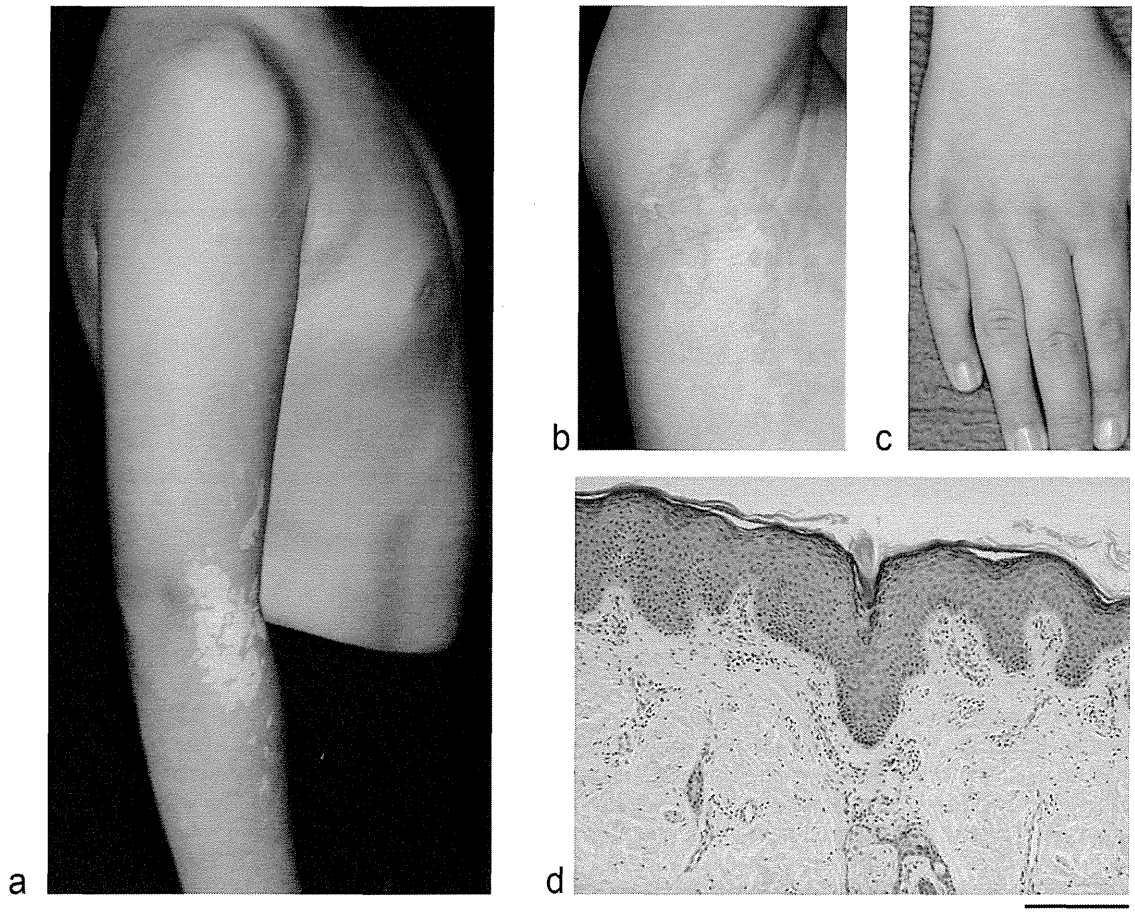

Fig. 1. (a–c) The dermatosis consisted of hyperkeratotic streaks with a bilateral, asymmetrical distribution following Blaschko's lines. (d) A cornoid lamella overlying a hair follicle was present. Bar: 150 μm

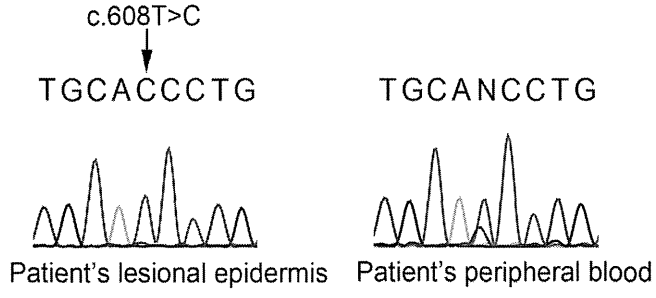

Fig. 2. Mutation analysis of *GJB2* in the patient's epidermis and peripheral blood. Direct sequencing of *GJB2* derived from the patient's lesional epidermis revealed a homozygous or monoallelic variant c.608T > C, although the PCR product from the patient's peripheral blood showed both wild type and variant alleles.

Funding sources

None.

Conflict of interest

We have no conflict of interest to declare.

Acknowledgements

The authors thank Ms. Haruka Ozeki and Ms. Yuka Terashita for their technical help in analysing *GJB2* mutations. This study was supported in part by a Grant-in-Aid for Challenging Exploratory Research 26670526 (to K.S.) and a Grant-in-Aid for Scientific Research (A) 23249058 (to M.A.) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and by the grant H26-itaku (nan)-ippan-027 (to K.S.) from the Ministry of Health, Labour, and Welfare (Research on Measures for Intractable Disease), Japan.

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Please cite this article in press as: K. Noda, et al., Porokeratotic eccrine ostial and dermal duct nevus with a somatic homozygous or monoallelic variant of connexin 26, J Dermatol Sci (2015), http://dx.doi.org/10.1016/j.jdermsci.2015.07.003

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Received 31 March 2015
Received in revised form 18 June 2015
Accepted 8 July 2015

Journal of Dermatological Science xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

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Genetic analyses of oculocutaneous albinism types 2 and 4 with eight novel mutations

Oculocutaneous albinism (OCA), inherited as an autosomal-recessive trait, is characterized by reduction or absence of melanin in the skin, hair, and eyes. OCA patients show symptoms such as reduced skin and hair pigmentation and consequent photosensitivity, high risk of skin cancer, and reduced visual acuity and nystagmus [1]. OCA is broadly classified into two groups: non-syndromic and syndromic, based on the presence of other symptoms such as bleeding diathesis, immunodeficiency, or neurological dysfunction [2]. OCA type 2 (OCA2, Online Mendelian Inheritance in Man [OMIM] #203200) caused by mutations in *P (OCA2)* [3] is the most common type of OCA worldwide (accounting for approximately 50% of all patients with OCA); however, the frequency among Japanese OCA patients is less than 10% [1]. On the other hand, OCA type 4 (OCA4, OMIM #611409) caused by mutations in *SLC45A2* [4] is rare worldwide, while in Japanese OCA patients, the frequency of OCA type 4 is approximately 30% [5]. Both, OCA2 and SLC45A2 proteins contain 12 putative transmembrane domains and are thought to function as transporters. Most pathological missense substitutions for albinism are located within or in close proximity to these domains [1], indicating that they play a critical role in overall protein function. These two subtypes show high clinical heterogeneity, from mild to severe hypopigmentation and a genotype-phenotype relationship has been previously reported. For example, p.A481T mutation in *OCA2*, located distal to the transmembrane domain, is reportedly associated with the mild phenotype. This pathogenic variant, which has 70% melanogenesis activity, has been found in not only OCA2 patients but also in approximately 12% of normally pigmented Japanese [1]. Recent investigations on *OCA2* in the Japanese population have also shown that p.A481T and p.H615R substitutions significantly contribute to skin color and are associated with risk of skin cancer [6,7]. Meanwhile, Shimanuki et al. [8] indicated that some *OCA2* variations including p.A481T, may have developed via diversifying selection.

We had the opportunity to examine seven Japanese patients with non-consanguineous parents, who were clinically diagnosed with OCA. Informed consent and blood samples were obtained following protocols approved by the Ethics Committee of Yamagata University, Faculty of Medicine. Samples were screened for *TYR* (OCA1), *P* (OCA2), *TYRP1* (OCA3), *SLC45A2*(OCA4), and *HPS1*(HPS1) mutations using single-strand conformation polymorphism/heteroduplex and direct sequencing techniques as previously described [5]. This analysis allowed us to genetically diagnose the subtypes of OCA and resulted in the detection of eight novel mutations (Table 1). These mutations included two splice-site mutations, IVS13 + 1(c.1364 + 1)G > A and IVS19 + 1(c.2079 + 1)G > A in *OCA2* (GenBank Accession number: NM_000275.2); five missense mutations, (c.125T > C, p.M42T; c.149C > T, p.A50V; c.157G > C, p.A53P; c.170C > T, p.T57I; and c.217G > T, p.V73L); and one nonsense mutation, c.1030C > T, p.Q344X in *SLC45A2* (GenBank Accession number: NM_016180.3). The newly identified mutations were not found in 100 unrelated, normally pigmented Japanese adults and were not identified in the 1000 Genomes Project and single nucleotide polymorphism (dbSNP, Build 142) databases. We confirmed that all the amino acids altered by these missense mutations were conserved among species including chimpanzee, monkey, cow, mouse, chicken, zebrafish, and frog. In addition, the novel missense mutations in *SLC45A2*, all of which were located within the transmembrane domain, were analyzed by nine different algorithms used to evaluate the functional impact of a variation: SIFT, PolyPhen2 based on HumanDiv and HumanVar models, LRT, Mutation Taster, Mutation Assessor, FATHMM, MetaSVM and MetaLR scores provided by dbNSFP 2.3 [9]. At least seven of the nine algorithms predicted these variations to be "damaging" or "probably damaging" (9/9: p.A50V, p.A53P, p.T57I; 8/9: p.M42T; 7/9: p.V73L). These findings indicated that the mutations are likely not polymorphisms and are probably pathological. Patients carrying these mutations (patients 3–6 showed compound heterozygous missense mutations) revealed some phenotype heterogeneity, indicating that aberrant proteins induced by missense substitutions resulted in variable loss of functional activity.

In addition, in the two cases with splice-site mutations in *OCA2*, we investigated effects of nucleotide changes at the splice site on the pre-mRNA splice pattern, using reverse-transcriptase polymerase chain reaction (RT-PCR) with RNA extracted from peripheral blood as previously described [10]. The primers used for RT-PCR were EX11cf (5′ CATGTGGTGGAGTGGATTGA 3′) and EX15cr (5′ AGTGAATCCGGCAAAGTCC 3′) for samples from patient 1, and EX18cf (5′ CAAATGCCTGACAGTGTTGG 3′) and EX21cr (5′ GGTAGCAGTGAACGGGATGT 3′) for samples from patient 2. DNA sequencing of the RT-PCR product of the samples obtained from patient 1 revealed a 92-nucleotide addition within exon 13 (Fig. 1a), predicted to cause a frameshift that encoded a truncated peptide with an additional 43-amino-acid peptide (p.R455fsX499). In patient 2, a skipping of exon19 was confirmed (Fig. 1b). This skipping is predicted to result in a frameshift and a truncated protein with an additional 45-amino-acid peptide (p.G651fsX697). Interestingly, one allele from patient 1 with relatively mild phenotype contained two missense substitutions (p.R10W and p.A481T) inherited from her mother, while another allele contained a splicing mutation that would result in a frameshift and a truncated protein, indicating the former allele retained some functional melanogenesis activity despite the combination of two pathological substitutions.

http://dx.doi.org/10.1016/j.jdermsci.2015.10.014

Table 1
Mutation and phenotype analysis for seven OCA patients.

Patient	Albinism/gene	Age at diagnosis	Sex	Mutation		Phenotype			
				Paternal	Maternal	Hair color	Iris color	Nystagmus	Skin color
1	OCA2/*P*	10 months	M	c.28C > T,p.R10W c.1441G > A, p.A481T	**IVS13 + 1G > A**	Blond	Brown	Negative	Lighter than normal
2	OCA2/*P*	3 months	F	c.1441G > A, p.A481T **IVS19 + 1G > A**	c.1441G > A, p.A481T	Blond	Gray	Negative	White, pink as baby
3	OCA4/*SLC45A2*	2 years	F	**c.125T > C, p.M42T**	**c.149C > T, p.A50V**	Blond	Brown	Negative	Lighter than normal
4	OCA4/*SLC45A2*	6 months	F	c.469G > A, p.D157N	**c.157G > C, p.A53P**	White	Gray	Positive	Creamy white
5	OCA4/*SLC45A2*	1 year	F	**c.170C > T, p.T57I**	c.469G > A, p.D157N[a]	Blond	Brown	Negative	Lighter than normal
6	OCA4/*SLC45A2*	4 years	M	c.265G > A, p.G89R	**c.217G > T, p.V73L**	Blond	Hazel	Negative	Lighter than normal
7	OCA4/*SLC45A2*	1 year	F	**c.1030C > T, p.Q344X**	c.469G > A, p.D157N	Blond	Gray	Positive	White, pink as baby

Novel mutations are in bold.
[a] Paternal and maternal origins were not determined.

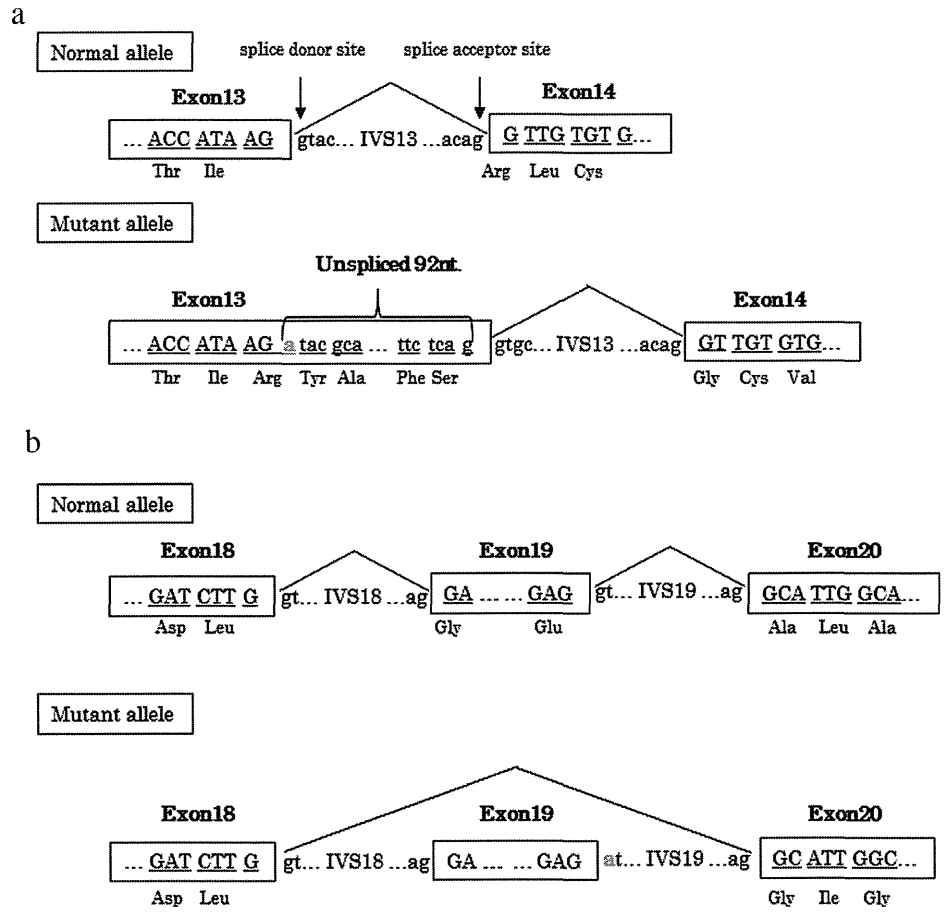

Fig. 1. RT-PCR analysis of *OCA2*in patient 1 and 2. (a) In patient 1, IVS13 + 1G > A mutation causes aberrant splicing adding 92 nucleotides within exon 13, predicted to result in a frameshift that encoded a truncated peptide with an additional 43-amino-acid peptide (p.R455fsX499). (b) In patient 2, a skipping of exon19 in mutant allele (IVS19 + 1G > A) was confirmed. This skipping is predicted to cause a frameshift and a truncated protein with an additional 45-amino-acid peptide (p.G651fsX697).

In conclusion, we detected eight novel mutations in Japanese patients with OCA2 and OCA4. These results may provide an insight into the unknown mechanism(s) of melanogenesis in humans.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

We are grateful to the patients, their families and volunteers for providing blood samples. This work was supported by a grant from the Ministry of Health, Labor, and Welfare of Japan (Health and Labor Sciences Research Grants; research on intractable diseases; H24-039) and a grant (22591236) from the Ministry of Education, Sports, Culture, Science, and Technology of Japan to T.S.

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Received 5 September 2015
Received in revised form 7 October 2015
Accepted 20 October 2015

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/1346-8138.13204

Journal of Dermatology 2016; **43**: 286–287

LETTER TO THE EDITOR

Unilateral generalized linear porokeratosis with nail dystrophy

Dear Editor,

Porokeratosis is a disorder of abnormal keratinization characterized clinically by well-defined annular lesions with hyperkeratotic ridges. Here, we report a case of unilateral generalized linear porokeratosis with dystrophy of the toenail.

A 36-year-old man showed unilateral, brownish-red plaques and round macules on the right side of his trunk and the right extremities, with slight itching (Fig. 1a). The eruptions had been present since childhood. At elementary school age, toenail dystrophy occurred after the appearance of cutaneous hyperkeratotic lesions. The lesions consisted of multiple pigmented hyperkeratotic and verrucous papules and plaques with a sharply demarcated border in a linear distribution. The lesions were distributed along the lines of Blaschko (Fig. 1a). Some of the macules had coalesced, and in some parts of the lesions, annular macules with hyperkeratotic rims were also seen. The linear lesions on the right leg were connected to the lesions in the toes. The nail of the right first toe was dystrophic and showed irregular grooving and pterygium (Fig. 1b,c). No bony abnormality of the affected toe was detected by X-ray examination (Fig. 1d). The patient had no cutaneous lesions on the hands. No nail dystrophy was seen on any finger. There were no mucosal or visceral abnormalities. He had neither immunosuppression nor any systemic disease associated with porokeratosis. He had no family history of porokeratosis.

Skin biopsies were taken from affected sites of the abdomen and the leg. Cornoid lamellae were found in the interfollicular epidermis (Fig. 1e).

From these clinical and histopathological findings, this case was diagnosed as linear porokeratosis.

Two forms of linear porokeratosis exist. In the rare generalized form, the lesions are multiple, and they affect several extremities and involve the trunk. Unilateral generalized linear porokeratosis is extremely rare.[1]

Nail involvement in linear parakeratosis is rare. To date, there have been only a few case reports of onychodystrophy in linear porokeratosis.[2,3] In one case, there was bony narrowing of the digits.[3] Six main variants of porokeratosis have been described.[4] In those variants, nail involvement was reported not only in linear porokeratosis, but also in porokeratosis of Mibelli[4] and porokeratosis plantaris palmaris et disseminata.[5] Though the exact pathogenesis of dystrophic nail is not yet understood, it is possible that nail changes occur through the involvement of the nail matrix and nail bed by atypical hyperproliferative keratinocytes, ultimately resulting in destruction of the whole nail.[2] Cases with nail involvement in linear porokeratosis are not as rare as those in the other porokeratosis variants. We speculate that this is because many cases of linear porokeratosis involve the distal portions of the extremities.

Local porokeratosis can be treated by topical therapy, such as with 5-fluorouracil, vitamin D_3 analogs, imiquimod or tretinoin creams.[4] For generalized porokeratosis, topical therapies may show variable effectiveness, but they are not practical. Therefore, systemic retinoids were anecdotally used for diffuse porokeratosis.[1] Our patient declined etretinate, the only internal retinoid available in Japan.

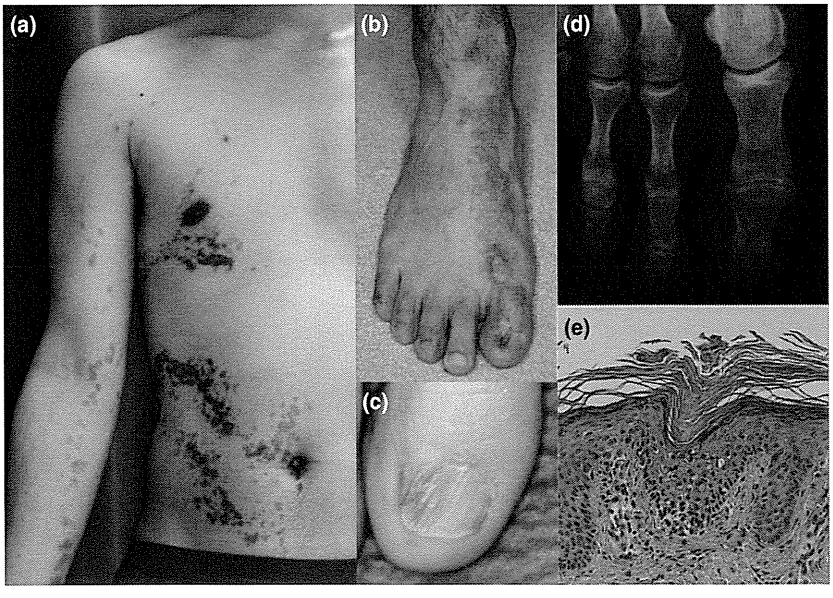

Figure 1. Unilateral generalized linear porokeratosis with nail dystrophy. The clinical and histopathological features of the current case. (a) A clinical photograph indicating the distribution pattern of the lesions. (b) A clinical photograph of the continuous linear lesion from the right dorsum of the foot to the toenail. (c) Nail dystrophy and pterygium on the right hallux next to the lesion. (d) An X-ray photograph of the affected toe shows no bony abnormalities. (e) A microphotograph of hyperkeratosis and a cornoid lamella in the interfollicular epidermis (hematoxylin–eosin stain, original magnification ×200).

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To our knowledge, this case is the first report of unilateral generalized linear porokeratosis with nail dystrophy.

CONFLICT OF INTEREST: None declared.

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Hyper-IgE syndrome with a novel mutation of the *STAT3* gene

doi: 10.1111/ced.12865

Hyper-IgE syndrome (HIES) is a primary immune deficiency characterized by atopic dermatitis (AD)-like skin lesions, extremely high serum IgE levels, and increased susceptibility to bacterial and fungal infections.[1] Recent studies have revealed that most cases of HIES are caused by mutations in the signal transduction and activation of transcription 3 gene (*STAT3*).[1] We report a patient with HIES manifesting intractable eczematous eruptions with xerosis, who had a novel mutation in the *STAT3* gene.

An 11-year-old Japanese girl presented with erythematous skin eruptions. Reddish papules and pustules were noted on both axillae (Fig. 1a), and the scalp was covered with scaly erythematous plaques. Paronychia and fingernail deformities were seen (Fig. 1b), and severe xerosis was noted over the whole body.

The skin eruption had first been noted when the child was 1 month of age. At 3 months of age, she had been admitted to hospital with pyoderma and measles, and histology had shown pulmonary infiltration with eosinophilia. Since then, the patient had repeatedly experienced lung abscesses, phlegmon and otitis media.

Laboratory investigations showed that T-cell counts, numbers of CD4-positive and CD8-positive cells, and CD4/CD48 ratios were normal. Analysis of the patient's peripheral blood using flow cytometry revealed slightly raised B cell counts. Serum IgE levels were also raised (6700–8800 U/mL; normal range < 170 U/mL).

HIES was considered because of the combination of raised IgE levels, eosinophilia (3–22%; normal range 0–10%), recurrent cutaneous abscess formation, infection, pneumonia with pneumatocele formation, and progressive coarsening of the facial features (Fig. 1c).

We carried out a genetic study on the patient. The study was approved by the ethics review committee of Nagoya University School of Medicine and all participants (or guardians) gave fully informed consent.

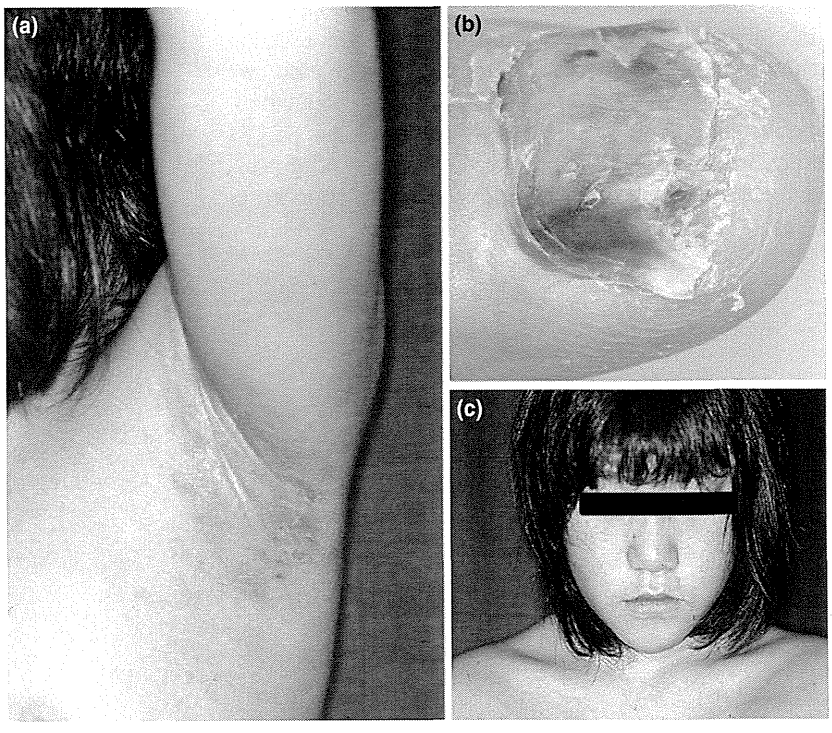

Figure 1 (a) Erythematous skin lesions on the bilateral axillae, with dry skin on the chest and the limbs; (b) bacterial paronychia on the finger; and (c) the characteristic leonine face of hyper-IgE syndrome.

We performed mutation analysis of *STAT3* to confirm the diagnosis, and detected a novel pathogenic mutation, c.1397A>T (p.N466S). We also searched for mutations of the filaggrin gene (*FLG*), which are important predisposing factors for AD. We screened for almost all the *FLG* mutations that are specific to the Japanese population,[2] but no population-specific mutations were noted in this case.

The patient was treated with hydrocortisone cream and antimycotic drugs, but minimal improvement was obtained, and the eczema and intense (possibly fungal) infection continued. Linezolid was then administered, which produced an excellent response of the fingernail deformities.

Dominant-negative mutations in *STAT3* account for the majority of autosomal and sporadic HIES cases.[1] Because the STAT3 protein plays an important role in signal transduction induced by many cytokines, including interleukin (IL)-6, IL-10, IL-17, IL-21 and IL-22, its deficiency results in upregulation and downregulation of pro-inflammatory and anti-inflammatory responses, leading to characteristic immunological abnormalities and infections.[3] However, the molecular mechanisms of these phenotypes have not been clarified completely.

In our case, we found a pathogenic mutation c.1397A>T (p.N466S) in *STAT3*. Although two other mutations, c.1396A>G (p.N466D) and c.1398C>G (p.N466K) were reported previously in this residue, the present mutation in N466S is novel.[4] This residue might be crucial for the function of STAT3.

Our patient had severe xerosis and eczematous eruptions, which are also seen in patients with AD. Mutations in *FLG* are frequently found in patients with AD. Filaggrin is a major structural protein in the stratum corneum of the epidermis and plays a key role in the barrier function of the skin.[2] The disruption of the barrier function causes severe xerosis in AD. In the present case, we searched for mutations in *FLG*, but found no population-specific mutations in our case. Therefore, the STAT3 deficiency itself might be related to expression of proteins and genes that are responsible for the barrier function of the skin. Investigation of the pathophysiology of HIES may help clarify the mechanisms of barrier dysfunction and dry skin in AD, and lead to development of new treatments.

Acknowledgements

This work was supported in part by grants-in-aid from the Ministry of Education, Science, Sports, and Culture of Japan (project 26860864, to S. Minakawa), and by the 2015 Hirosaki University Research Support System.

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Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 23 September 2015

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JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13308
Journal of Dermatology 2016; ●●: 1–2

LETTER TO THE EDITOR

Reticulate acropigmentation of Kitamura with a novel *ADAM10* mutation: A case report

Dear Editor,

Reticulate acropigmentation of Kitamura (RAK) is a rare genetic disorder with an autosomal dominant pattern of inheritance with high penetrance.[1] In 2013, the causative gene of RAK was clarified as a disintegrin and metalloproteinase domain-containing protein 10 gene (*ADAM10*).[1] Here, we report a case of RAK with a novel *ADAM10* mutation.

A 43-year-old Japanese woman visited our department for diagnosis of reticular hyperpigmented macules that had been present on the dorsal aspect of the hands and feet for 34 years and on the extensor surfaces of the knees for 5 years (Fig. 1a–c). Palmar pits were also present (Fig. 1d). She stated that her mother had similar pigmented macules (Fig. 1e). Laboratory tests were within normal limits, including liver, kidney and thyroid functions. Levels of serum adrenocorticotropic hormone, cortisol and porphyrin were also within normal limits. Serum antinuclear antibodies were negative. A skin biopsy obtained from reticular hyperpigmented macules on the right lateral malleolus showed elongation and thinning of the rete ridges and hyperkeratosis without parakeratosis, and

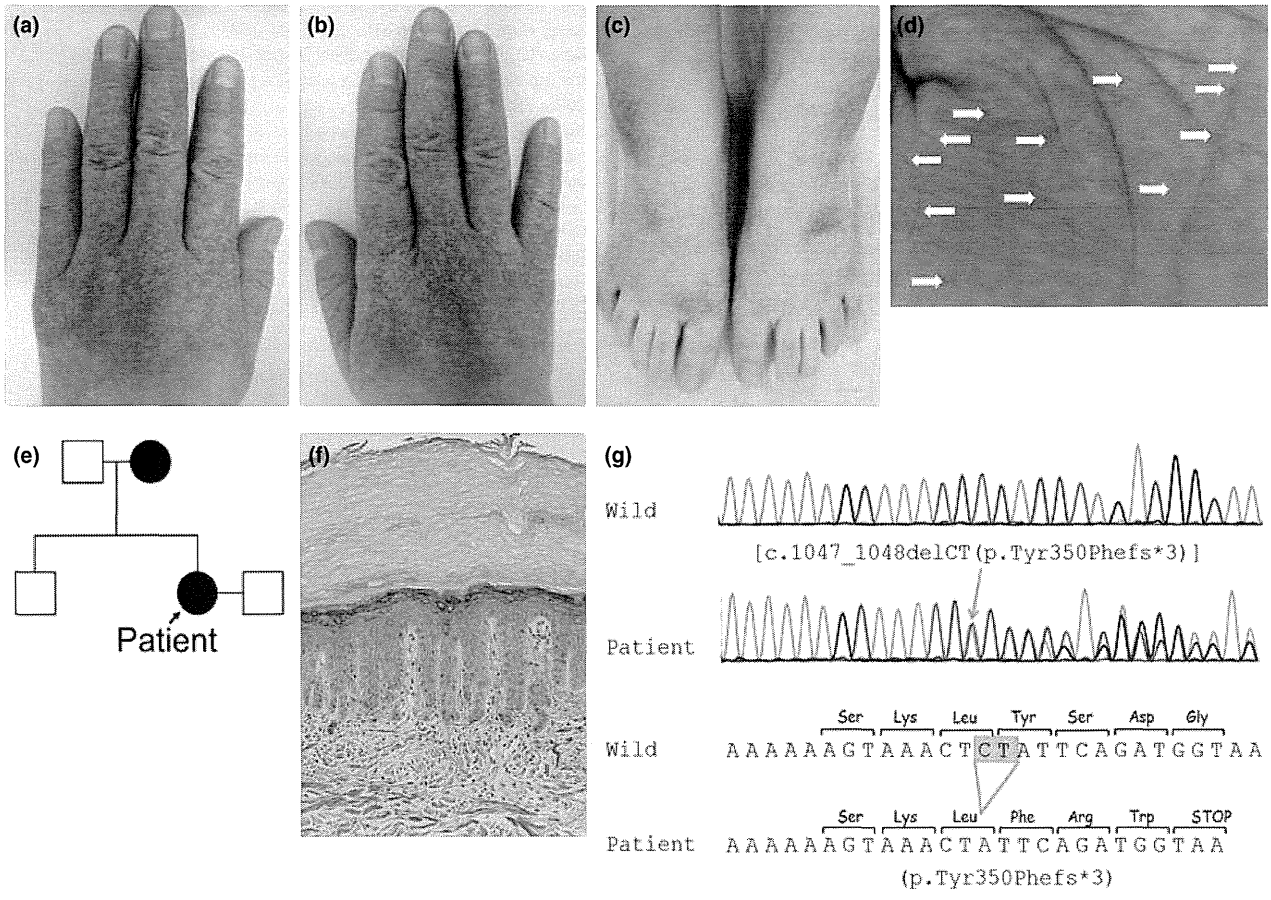

Figure 1. Clinical photographs, family tree, histopathological study and *ADAM10* sequence data of the patient. (a–c) Hyperpigmented macules in a reticular pattern on the dorsal aspect of the hands and feet. (d) Arrows indicate pits on the left palm. (e) White square, male without reticulate acropigmentation of Kitamura (RAK); black circle, female with RAK. (f) A skin biopsy obtained from reticular hyperpigmented macules on the right lateral malleolus showed elongation and thinning of the epidermal rete ridges with hyperkeratosis, basal hyperpigmentation and epidermal atrophy (hematoxylin–eosin, original magnification ×100). (g) Arrow indicates heterozygous c.1047_1048delCT (p.Tyr350Phefs*3).

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pigmentation in the tip of rete ridges. A few inflammatory cell infiltrates were seen in the dermis (Fig. 1f). Following ethical approval, informed consent was obtained from the patient in compliance with the Declaration of Helsinki principles. Genomic DNA was extracted from her blood samples. All coding regions and flanking sites of the *ADAM10* (NM_001110.2) were amplified by polymerase chain reaction and Sanger sequencing was performed as in a previous report.[1] As a heterozygous c.1047_1048delCT (p.Tyr350Phefs*3) in *ADAM10* was confirmed (Fig. 1g), we diagnosed this case as RAK.

In our case, the clinical and histopathological differential diagnosis included Dowling–Degos disease (DDD). RAK is clinically characterized by reticulate, brown-pigmented macules primarily localized to the dorsal surface of the hands and feet in association with palmar and plantar pits.[1] DDD is characterized by a postpubertal reticulate hyperpigmentation and small hyperkeratotic dark-brown papules that mainly affect the flexures and great skin folds.[2] Histopathologically, acanthosis with tight digitiform rete ridges is seen in the skin lesions of DDD, and thinning of the epidermis and narrowing of the rete ridges characterize the skin lesions of RAK.[3] The keratin 5 gene (*KRT5*),[2] protein O-fucosyltransferase 1 gene (*POFUT1*)[4] and protein O-glucosyltransferase 1 gene (*POGLUT1*)[5] were identified as the causative genes of DDD. A study of six RAK and five DDD patients whose diagnosis was confirmed by mutation analysis revealed that RAK and DDD are two distinct entities clinically and histologically.[3] In this context, clinical and histopathological features of the present case were typical for RAK, not DDD. In addition, the diagnosis was confirmed by the mutation analysis.

In the present case, the gene mutations as well as the clinical and histopathological features supported the diagnosis of RAK. However, the pathogenesis of RAK with *ADAM10* mutation has not been elucidated completely yet. Therefore, further accumulation of the cases is thought to be required.

CONFLICT OF INTEREST: None declared.

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LETTER TO THE EDITOR

Hyperpigmentation over the metacarpophalangeal joints and the malleoli in a case of hyaline fibromatosis syndrome with *ANTXR2* mutations

Editor

Hyaline fibromatosis syndrome (HFS) is a rare autosomal recessive disorder characterized by multiple subcutaneous skin nodules, gingival hypertrophy, joint contractures and hyaline deposition. Mutations in the anthrax toxin receptor 2 (ANTXR2) gene (*ANTXR2*) underlie HFS.[1,2] Although several cutaneous findings were documented, hyperpigmentation over the joints in HFS was not emphasized. Here, we report an infant with HFS with hyperpigmentation over the metacarpophalangeal joints and the malleoli as an initial cutaneous finding.

A 2-month-old Japanese girl presented at our clinics with painful arthrogryposis of the large joints. She was born to healthy non-consanguineous parents. She never raised her hands and seemed to have pain since birth when her large joints experienced excessive pressure. Clinical findings at 2 months of age were as follows: neurologically, she showed pursuit and cradling laughter. Moro reflex was negative. Grasp reflex, sucking reflex and deep tendon reflex were all diminished. Flexion contractures affecting the elbows, hips and knees resulted in painful and restricted passive movements. In addition to thickened, stiff skin in part, hyperpigmentation over her metacarpophalangeal joints and malleoli was observed (Fig. 1a–d). Laboratory examinations including blood cell counts and biochemistry were normal. Circulating antinuclear antibodies were negative. Screenings for congenital metabolic disorders were negative. An electromyogram and nerve conduction studies were normal. At 6 months of age, low serum protein concentration (3.6 g/dL) and low serum albumin concentration (1.9 g/dL) were noted in her peripheral blood. Faecal α1-antitrypsin concentration was high. Thus, protein-losing enteropathy or intestinal malabsorption was considered. At 10 months of age, skeletal radiography revealed osteopenia, periosteal reaction, and lucent lesions in the proximal phalanges of the fingers and toes, distal end of the ulna and the ilium. At that time, the hyperpigmentation over her metacarpophalangeal joints and malleoli, and painful arthrogryposis of the large joints, had progressed. Furthermore, gingival hyperplasia occurred. At 17 months of age, gastroscopy and small intestinal biopsy were performed. Pathological findings of the biopsy specimen showed amorphous eosinophilic fibres in the lamina propria mucosa and submucous tissue with haematoxylin eosin staining. The amorphous eosinophilic fibres were stained by periodic acid-Schiff stain.

Following the ethics board approval, informed written consent was obtained in compliance with the Declaration of Helsinki guidelines. The coding regions of *ANTXR2*, including the exon–intron boundaries, were amplified from genomic DNA by polymerase chain reaction (PCR), as described elsewhere.[2] The patient had compound heterozygous *ANTXR2* mutations c.*1294C*>T (p.Arg432X) at exon 15 and c.1073_1074insC (p.Pro358Profs13X) at exon 13 (Fig. 2). Her father and mother had a heterozygous *ANTXR2* mutation, c.1294C>T and c.1073_1074insC respectively. c.1294C>T was previously reported as a disease causative mutation of HFS.[3] c.1073_1074insC is one of the recurrent hotspot frameshift mutations at exon 13, which cause HFS.[3] Therefore, the patient was diagnosed as HFS with mutations of *ANTXR2*.

The predominant cutaneous findings of HFS are thickened, stiff skin; small nodules of the perianal region, ears and lips; and a reddish-blue discoloration overlying the joints.[4] In the present case, hyperpigmentation over the metacarpophalangeal joints and the malleoli was prominent at 2 months of age. Hyperpigmentation over the same joints was demonstrated in Hispanic cases of HFS at 5–14 months of age.[3,4] Interestingly, all three Hispanic cases and our Japanese case with hyperpigmentation had bi-allelic truncating *ANTXR2* mutations.[4] Further investiga-

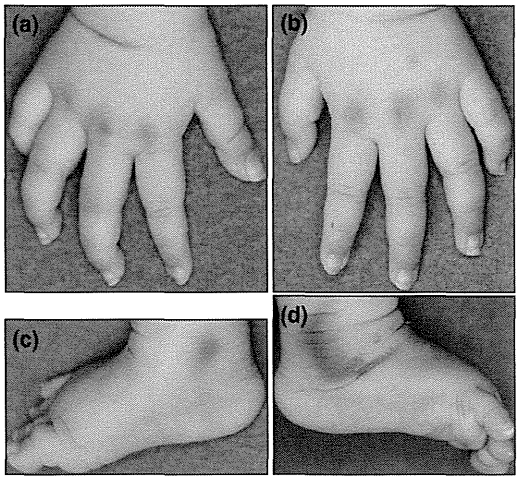

Figure 1 Hyperpigmentation over the joints in the patient at 4 months of age. Hyperpigmentation over the metacarpophalangeal joints (a, b) and the malleoli (c, d) was observed.