Fig. 2 (a) Direct DNA sequencing of exon 6 of *LDHA* gene, showing a 20 bp deletion in exon 6. (b and c) Intracytoplasmic cytokine analysis, showing that the frequencies of IL-17A$^+$CD8$^-$ cells (representing IL-17A$^+$CD4$^+$ T cells) and IL-22$^+$CD8$^-$ cells (representing IL-22$^+$CD4$^+$ T cells) were 23.3% and 15.4%, respectively, in case 1. (d and e) ELISA data of the serum levels of chemerin and IL-8 in case 2, which are significantly higher than those in a healthy subject (*$P = 0.022$ and $P = 0.015$, respectively). Ctr: control; Pt: patient

Fig. 1

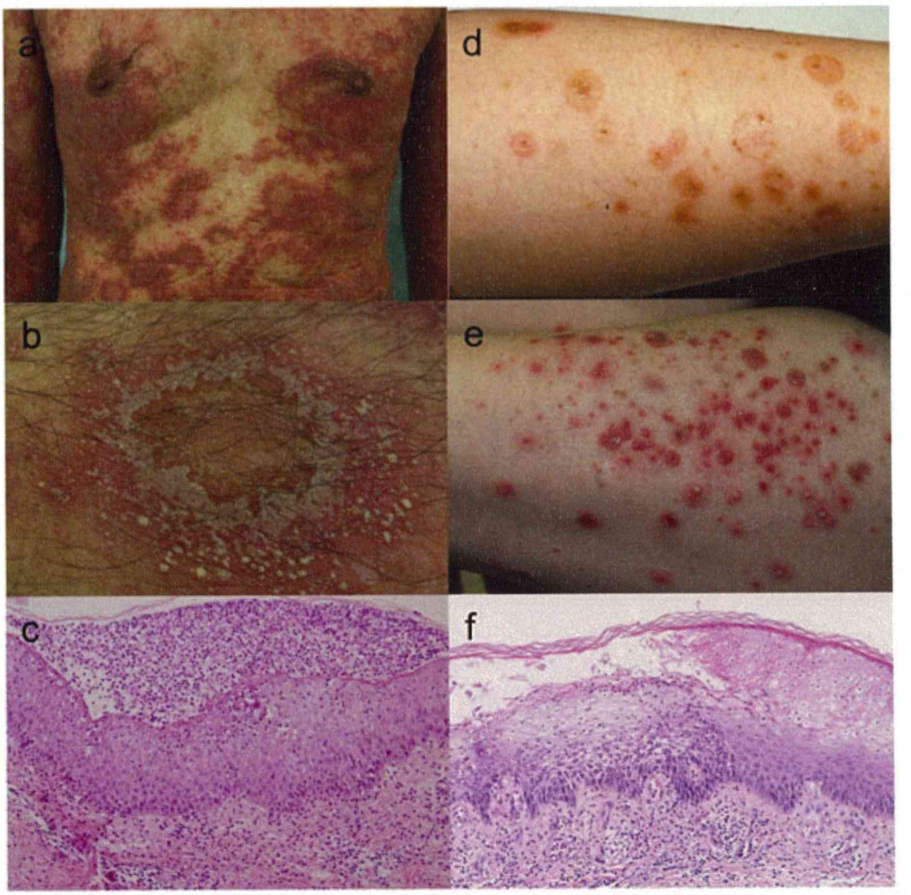
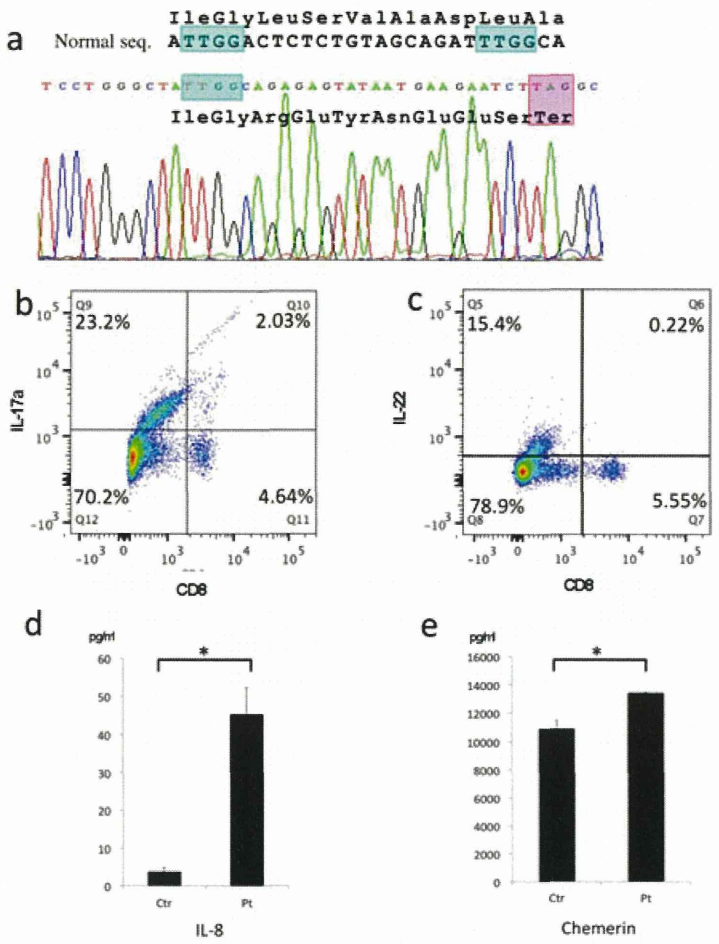


Fig. 2



Case Report/Case Series

Acute Generalized Exanthematous Pustulosis Caused by Dihydrocodeine Phosphate in a Patient With Psoriasis Vulgaris and a Heterozygous *IL36RN* Mutation

Noriaki Nakai, MD, PhD; Kazumitsu Sugiura, MD, PhD; Masashi Akiyama, MD, PhD; Norito Katoh, MD, PhD

IMPORTANCE Acute generalized exanthematous pustulosis (AGEP) is a rare and severe type of drug eruption. Dihydrocodeine phosphate is a semisynthetic opioid analgesic. Recently, recessive mutations in *IL36RN* have been identified in generalized pustular psoriasis (GPP). To date, 4 cases of AGEP and *IL36RN* mutation without previous history of psoriasis vulgaris (PV) have been reported.

OBSERVATIONS A woman in her 60s with PV presented with diffuse erythema, nonfollicular pustules, and fever. She had been treated with dextromethorphan hydrobromide hydrate, amoxicillin hydrate, clarithromycin, dihydrocodeine phosphate, tipepidine hibenzate, and tulobuterol tape for a cough and common cold. Based on histopathologic results and a positive result in a drug provocation test with dihydrocodeine phosphate, she was diagnosed with AGEP. A heterozygous *IL36RN* mutation c.28C>T (p.Arg10X) was also confirmed by mutation analysis.

CONCLUSIONS AND RELEVANCE This is the first report of dihydrocodeine phosphate–induced AGEP. In this case, helper T cells, type 17, might have been activated because of morphine and underlying PV, followed by increased production of interleukin (IL) 36. However, because of the *IL36RN* mutation, IL-36 signaling was uncontrolled, which might have resulted in the occurrence of AGEP. An *IL36RN* mutation might underlie several different pustular skin eruptions, including AGEP and GPP, and further accumulation of patient data is required.

JAMA Dermatol. doi:10.1001/jamadermatol.2014.3002
Published online November 19, 2014.

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Acute generalized exanthematous pustulosis (AGEP) is a rare and severe type of drug eruption. It is characterized by acute, extensive, sterile pinhead-sized nonfollicular pustules, erythema, edema, fever, and leukocytosis with neutrophilia.[1] Dihydrocodeine phosphate is a semisynthetic opioid analgesic used mainly in cough medicines in Japan.[2] Herein, we report the first case to our knowledge of AGEP caused by dihydrocodeine phosphate in a patient with psoriasis vulgaris (PV) and a heterozygous *IL36RN* mutation. We also discuss the possible causal mechanism of AGEP in this particular case.

Report of a Case

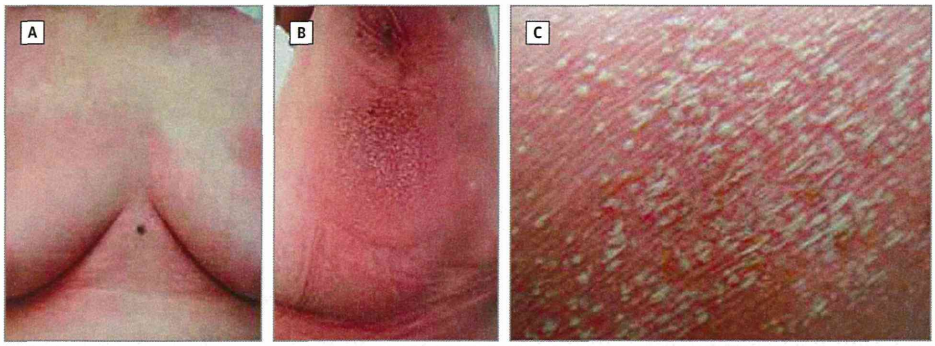
This study was approved by the Nagoya University Graduate School of Medicine institutional review board. Patient written informed consent was obtained, in compliance with the Declaration of Helsinki principles.

A woman in her 60s with a history of urticaria-type drug eruption caused by phenytoin consulted a physician about erythematous eruptions all over her body. At age 22 years, she had been diagnosed with PV and had been treated with topical steroids and topical vitamin D analogs. She had also been treated with oral nonsteroidal anti-inflammatory drugs (NSAIDs) for 10 years for arthralgia of the knees.

More immediately prior to presentation, she had been treated with dextromethorphan hydrobromide hydrate for 12 days, amoxicillin hydrate for 8 days, and clarithromycin, dihydrocodeine phosphate, tipepidine hibenzate, and tulobuterol tape for 2 days for a cough and common cold. Three days before presentation, she noticed the eruptions. Therefore, she stopped using clarithromycin, dihydrocodeine phosphate, tipepidine hibenzate, and tulobuterol tape of her own volition while continuing to take dextromethorphan hydrobromide hydrate and amoxicillin hydrate.

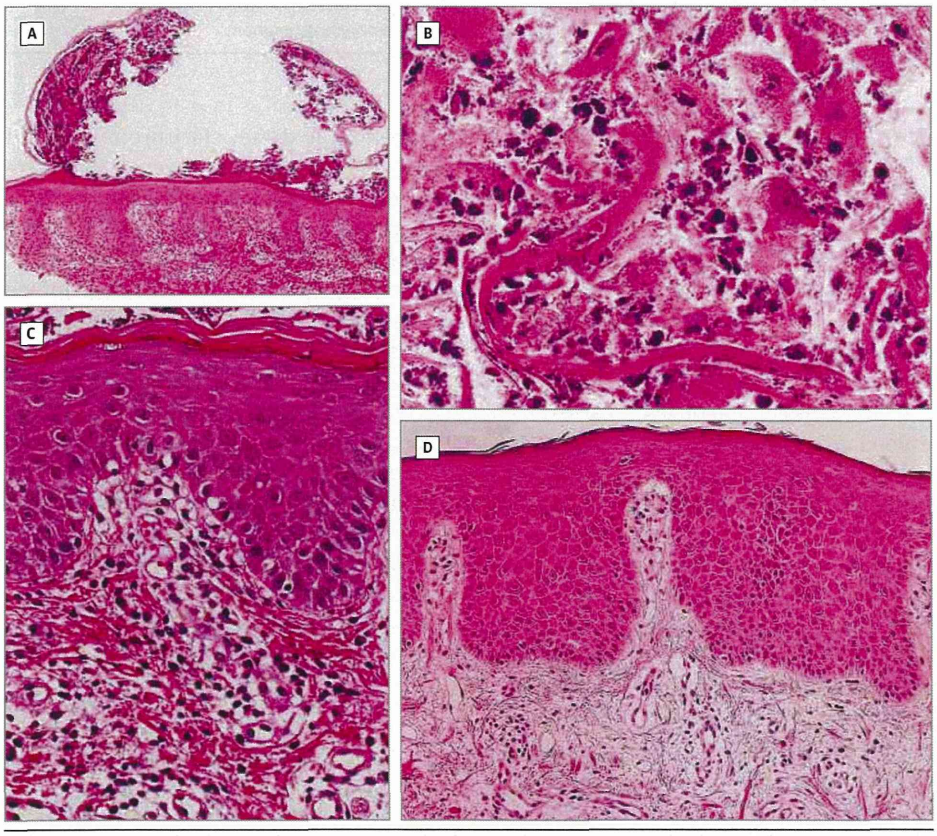
Initial physical examination revealed fever (temperature, 37.5°C) and diffuse erythema over the whole body with predominant localization in the intertriginous folds (**Figure 1**A). Hundreds of nonfollicular pustules on the erythema were diffusely spread over the upper arms and lateral chest areas (Figure 1B and C). The erythematous and scaly lesions on the

Figure 1. Clinical Findings at the First Visit



A, Diffuse erythema on the chest and abdomen. B, Diffuse erythema with pustules on the left lateral chest. C, A close-up view showing nonfollicular pustules.

Figure 2. Hematoxylin-Eosin-Stained Histopathologic Specimens From Erythema With a Pustule on the Chest and a Scaly Erythematous Lesion on the Neck



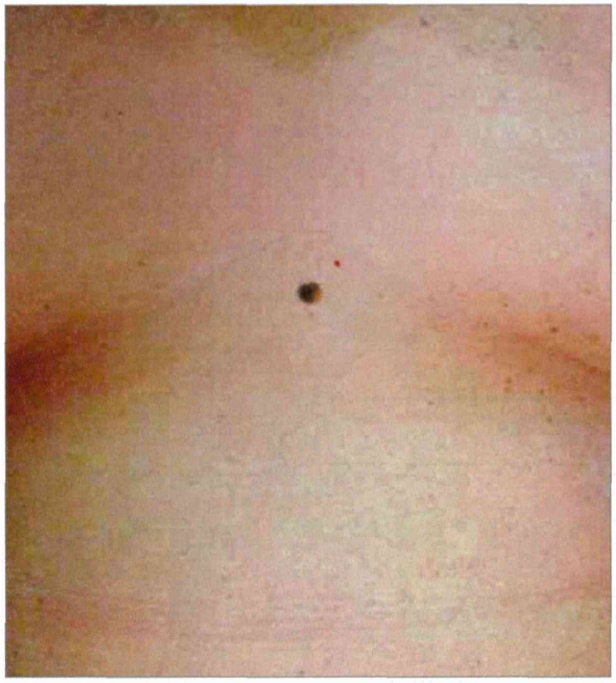
A-C, Chest specimens. A, Intracorneal pustule and epidermis showing mild elongation of rete ridges (original magnification ×40). B, Intracorneal pustule with large numbers of neutrophils (original magnification ×400). C, Thinned granular layer and a necrotic keratinocyte in the epidermis; liquefaction degeneration of the basal layer; and lymphocytic perivascular infiltrate with admixed neutrophils in the superficial dermis (original magnification ×200). D, Neck specimen, parakeratosis with thinning of the granular layer and hyperplasia of the epidermis with regular elongation of rete ridges and dilation and tortuosity of the blood vessels in the dermal papillae (original magnification ×100).

posterior region of the neck were consistent with PV. There were no mucosal lesions associated with Stevens-Johnson syndrome.

The white blood cell count (15 400/μL; normal range, 3400-7300/μL), including neutrophils (13 890/μL; normal range, 1214-5110/μL), and serum levels of C-reactive protein (CRP) (7.75 mg/dL; normal range, 0-0.2 mg/dL) were all elevated. (To convert white blood cells and neutrophils to number of cells × 10^9/L, multiply by 0.001; to convert CRP to nanomoles per liter, multiply by 9.524.) Liver and kidney function and eosinophil percentage were within normal limits. Lymphocyte transformation findings for amoxicillin hydrate (stimulation index, 1.5; normal, <1.8) and dihydrocodeine phosphate (stimulation index, 1.0; normal, <1.8) were negative. No microbial growth from cultures of pustules was seen.

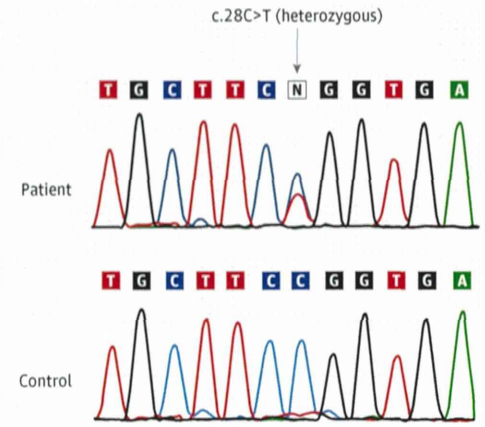
A biopsy specimen of the erythema with pustule on the left lateral chest showed an intracorneal pustule containing large numbers of neutrophils and epidermis with mild elongation of rete ridges (**Figure 2**A and B). High magnification showed a thin granular layer and a few necrotic keratinocytes in the epidermis, liquefaction degeneration of the basal layer, and lymphocytic perivascular infiltrate with admixed neutrophils in the superficial dermis. No Kogoj spongiform pustules were observed (Figure 2C). A biopsy specimen of the scaly ery-

Figure 3. Clinical Findings After a Drug Provocation Test



At 20 hours after taking dihydrocodeine phosphate at 1/10 therapeutic dose, diffuse erythemas were confirmed on the chest and abdomen.

Figure 4. *IL36RN* Sequence Data of the Patient



Arrow indicates c.28C>T (heterozygous) mutation.

thematous lesion on the posterior region of the neck showed parakeratosis with thinning of the granular layer and hyperplasia of the epidermis with regular elongation of rete ridges and dilation and tortuosity of the blood vessels in the dermal papillae, consistent with PV in a patient undergoing treatment with topical steroids and topical vitamin D analogs (Figure 2D).

On the basis of her history, clinical features, blood test results, and histologic findings, AGEP or generalized pustular psoriasis (GPP) was suspected. Treatment with all medications was stopped, and she was hospitalized.

In the hospital, she was treated with oral epinastine hydrochloride, 20 mg/d; topical clobetasone butyrate, 0.05%, on her neck; and difluprednate, 0.05%, on her trunk and extremities. The fever, pustules, and erythema resolved within 3, 5, and 12 days, respectively, and she was discharged.

In an outpatient setting, patch and scratch-patch tests were performed using dextromethorphan hydrobromide hydrate, 30%, amoxicillin hydrate, 10% and 20%, clarithromycin, 20%, dihydrocodeine phosphate, 1% and 10%, tipepidine hibenzate, 10% and 20% (all doses in petrolatum), and tulobuterol tape, according to the guidelines of the International Contact Dermatitis Research Group. All patch and scratch-patch test results were negative.

Subsequently, the patient was hospitalized, and oral challenge tests were performed using 1/10, 1/5, 1/2, and full therapeutic doses of dextromethorphan hydrobromide hydrate, amoxicillin hydrate, clarithromycin, and tipepidine hibenzate and a 1/10 therapeutic dose of dihydrocodeine phosphate. The test reactions to dextromethorphan hydrobromide hydrate, amoxicillin hydrate, clarithromycin, and tipepidine hibenzate were all negative. However, skin eruptions were reproduced over the whole body within 20 hours after taking dihydrocodeine phosphate at a 1/10 therapeutic dose (**Figure 3**). At this time, the body temperature and most laboratory test results were within normal limits, including findings of a complete blood cell count and tests for liver and kidney function, but serum levels of CRP (0.91 mg/dL) were slightly elevated. Based on these results, a diagnosis of AGEP caused by dihydrocodeine phosphate was made. The eruptions disappeared spontaneously within 6 days of the test, and the patient was discharged.

In an outpatient setting, DNA was extracted from venous blood samples. All coding regions and associated splice sites of the *IL36RN* locus were amplified by polymerase chain reaction, and Sanger sequencing was performed. A heterozygous mutation c.28C>T (p.Arg10X), which is one of the GPP-causing founder mutations in Japanese people, was confirmed (**Figure 4**).[3]

Discussion

To our knowledge, the present case and one described by Matsuzawa et al[2] are the only reports in the English language literature of drug eruptions induced by dihydrocodeine phosphate. In Matsuzawa et al.[2] the patient showed erythema multiforme major. AGEP is usually caused by penicillins, macrolides, pristinamycin, quinolones, chloroquine, antiinfective sulfonamides, terbinafine, diltiazem, carbamazepine, spiramycin, and metronidazole.[4] The main differential diagnosis is GPP,[4] and AGEP might be difficult to differentiate from GPP both clinically and histopathologically.[5] However, the presence of eosinophils, necrotic keratinocytes, and a mixed interstitial and mid-dermal perivascular infiltrate, and the absence of tortuous or dilated blood vessels, favor a diagnosis of AGEP.[5]

These findings, except the presence of eosinophils, correspond to those in the present case. According to the differentiation between AGEP and GPP,[1] the present case showed the history of PV, the predominant distribution pattern of the intertriginous folds, the shorter duration of pustules and fever, the history of drug reaction, the recent drug administration, and the histopathologic findings that all favored the diagnosis of AGEP rather than GPP. According to the AGEP validation score of the EuroSCAR study group,[1] the total score in the present case was 10 (pustules, +2; erythema, +2; distribution/pattern, +2; postpustular desquamation, +1; mucosal involvement, 0; acute onset, 0; resolution ≤15 days, 0; fever ≥38°C, 0; polymorphonuclear neutrophils ≥7000/μL, +1; and histology, +2) . Therefore, the present case was interpreted as definite AGEP. Because our patient had been treated with oral NSAIDs for arthralgia of the knees, the body temperature might not have risen above 38°C. From these results and the positive drug provocation test findings, we are confident that this is the first report of dihydrocodeine phosphate–induced AGEP.

Recently, recessive mutations in *IL36RN*, which encodes the anti-inflammatory interleukin (IL)-36 receptor antagonist (IL-36Ra), have been identified in GPP[3,6,7]; IL-36Ra blocks IL-36, including IL-36α, β, and γ. In the case of the *IL36RN* mutation, IL-36 signaling is uncontrolled, and enhanced production of IL-6, IL-8, IL-1α, and IL1β occurs.[8] Mutations in *IL36RN* are found in a majority of GPP cases not accompanied by PV and in about 10% of GPP cases accompanied by PV.[3] However, it is uncertain whether the mutation is also a marker for AGEP.

Navarini et al[9] have reported that these phenomena might give rise to pustular eruptions in GPP, and *IL36RN* mutations might also underlie some forms of AGEP. In their report, 4 patients with AGEP and *IL36RN* mutations without a history of PV were described. Three heterozygous (c.338C>T; c.338C>T; and c.142C>T) and 1 homozygous (c.80T>C) single-nucleotide substitutions in *IL36RN* were identified. The *IL36RN*-mutated cases were associated with exposure to amoxicillin in 2 cases, clindamycin-rifampicin in 1 case, and piroxicam in a case from the literature. In addition, our research group[10] has reported GPP triggered by amoxicillin in monozygotic twins with compound heterozygous *IL36RN* mutations.

Herein, we present a case of AGEP associated with exposure to dihydrocodeine phosphate in a patient with a heterozygous *IL36RN* mutation. This mutation might underlie several different pustular skin eruptions that can occur spontaneously or in association with exogenous factors such as drugs, as seen in the present case.

Interleukin 17 is closely associated with the pathogenesis of PV. Helper T (T_H) cells, type 17, are overrepresented in lesions from patients with PV, and lesional T_H17 cells produce IL-17 without stimulation.[11] The anti-IL-17 monoclonal antibody ixekizumab improves the clinical symptoms of PV.[12] Carrier et al[13] have reported increased gene expression of IL-36 in a T_H17-dominant psoriasislike animal model and in cultured primary human keratinocytes by IL-17A and tumor necrosis factor (TNF), and IL-22 synergized with IL-17A and TNF. Furthermore, IL-36 directly induced the production of proinflammatory mediators such as TNF, IL-6, and IL-8 in the keratinocytes.[13]

AGEP serves as a valuable model for characterizing T cells, with production of IL-8 leading to neutrophilic inflammation.[14] Opioid receptor agonists are known as modulators of innate and adaptive immune responses, and functional activity of T_H17 cells is significantly increased with chronic morphine exposure.[15]

In the present case, T_H17 cells may have been constantly activated because of the underlying PV. In addition, the T_H17 cells may have been further activated by morphine, a metabolic product of dihydrocodeine phosphate, followed by increased production of IL-36. However, because of the *IL36RN* mutation, IL-36 signaling was uncontrolled, and the production of proinflammatory mediators, such as IL-8, was induced by keratinocytes, which might have resulted in the occurrence of AGEP.

Conclusions

The pathogenesis of dihydrocodeine phosphate–induced AGEP with the *IL36RN* mutation is still unclear, and a singular case is insufficient to establish a clear explanation. Therefore, further accumulation of patient data, including data related to the *IL36RN* mutation, and careful observation of the clinical course are required to improve the understanding of AGEP associated with the *IL36RN* mutation.

ARTICLE INFORMATION

Accepted for Publication: August 9, 2014.

Published Online: November 19, 2014. doi:10.1001/jamadermatol.2014.3002.

Author Contributions: Dr Nakai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Nakai, Sugiura, Akiyama, Katoh.
Acquisition, analysis, or interpretation of data: Nakai, Sugiura, Akiyama.
Drafting of the manuscript: Nakai.
Critical revision of the manuscript for important intellectual content: Nakai, Sugiura, Akiyama, Katoh.
Administrative, technical, or material support: Nakai, Sugiura.
Study supervision: Sugiura, Akiyama, Katoh.

Conflict of Interest Disclosures: None reported.

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Acta Derm Venereol 2015; 95: 362–363

SHORT COMMUNICATION

Darier's Disease: A novel *ATP2A2* Missense Mutation at One of the Calcium-binding Residues

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Accepted Jun 30, 2014; Epub ahead of print Jun 30, 2014

Darier's disease (DD) is a rare autosomal dominantly inherited skin disorder caused by a heterozygous mutation in *ATP2A2*, which is expressed in both the skin and the brain and encodes for type 2 sarcoendoplasmic reticulum Ca-ATPase (SERCA2) (OMIM 124200). Gain of function due to Ca^{2+} leakage was suggested as the mechanism behind how the mutations cause DD (1). DD sometimes shows neuropsychiatric manifestations. Herein, we report a Japanese patient with DD, who has a novel mutation in one of the Ca^{2+}-binding residues (CBR) in the endoplasmic reticulum (ER) membrane. A review of the literature on *ATP2A2* mutations in CBR and DD phenotypes suggested differences between the mutations in terms of the accompanying symptoms.

CASE REPORT

A 40-year-old woman with no familial history of DD or other serious comorbidities was admitted. Physical examination showed reddish papules on her back and breast (Fig. 1A, B). Histopathology of the papule on the back revealed suprabasal acantholysis with corps ronds and grains (Fig. 1C). Treatment with etretinate effectively resolved the skin lesions.

Following ethical approval, informed written consent was obtained from the patient in compliance with the Declaration of Helsinki guidelines. The coding regions including exon-intron boundaries of *ATP2A2* were amplified from genomic DNA by PCR as described elsewhere (2). Direct sequencing of the patient's PCR products revealed the heterozygous missense mutation c.2721A>C (p. Glu907Asp) (Fig. 1D). The glutamine residue at 907, which plays an important role in Ca^{2+} transportation, was confirmed to be highly conserved in ATP2A2 from diverse mammalian species (Fig. S1A[1]). c.2721A>C was not detected in any of the 200 control alleles (100 control individuals) (data not shown). Thus, the patient was diagnosed as having DD with the heterozygous ATP2A2 mutation.

DISCUSSION

SERCA2 normally pumps Ca^{2+} from the cytoplasm to the ER. SERCA2 has 2 splice forms: SERCA2a and

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1927

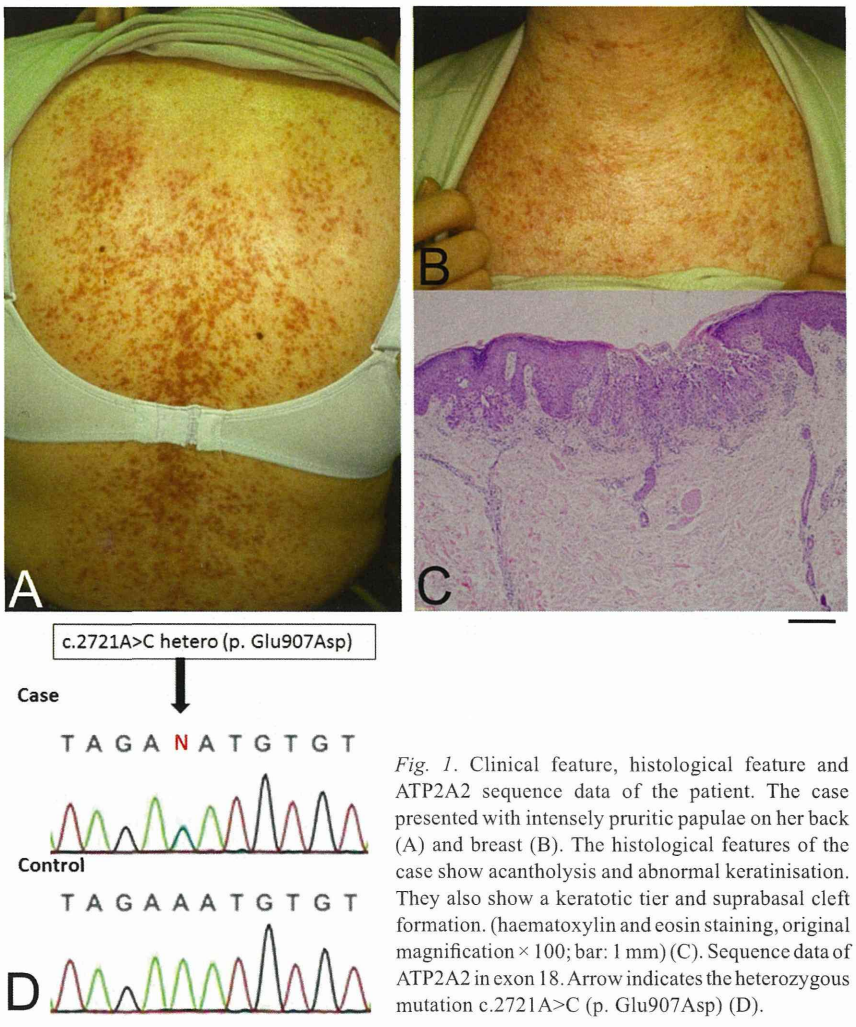

Fig. 1. Clinical feature, histological feature and ATP2A2 sequence data of the patient. The case presented with intensely pruritic papulae on her back (A) and breast (B). The histological features of the case show acantholysis and abnormal keratinisation. They also show a keratotic tier and suprabasal cleft formation. (haematoxylin and eosin staining, original magnification × 100; bar: 1 mm) (C). Sequence data of ATP2A2 in exon 18. Arrow indicates the heterozygous mutation c.2721A>C (p. Glu907Asp) (D).

SERCA2b. SERCA2a is restricted to the slow-twitch skeletal and cardiac muscles, whereas SERCA2b is ubiquitously expressed, and expressed especially highly in keratinocytes. SERCA2b has 11 ER transmembrane domains (TM) and 10 CBR. CBR is necessary for Ca^{2+} transport (Fig. S1B[1], Table SI[1]). Each CBR seems to have different levels of importance for Ca^{2+} transport (3).

Three mutations causing amino acid alterations of 2 CBR (p.Asn767 and p.Asn795) have been reported (Table SI[1]) (4–7). p.Asn767Ser was found in 4 cases of severe DD accompanied by neuropsychiatric symptoms or haemorrhages in the skin lesions, which suggests severe dysfunction of SERCA2 by the mutation. However, p.Asn767Asp is found in DD without accompanying symptoms. p.Asn795Ser was found in a DD patient whose phenotype was not described in detail. p.Glu907Asp, found in the present case, was the fourth mutation at CBR to be reported in the literature.

In conclusion, the present case and previous cases suggest that even missense *ATP2A2* mutations at CBR do not always cause severe DD with accompanying symptoms. This may be because each CBR differs in its importance to Ca^{2+} transport.

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