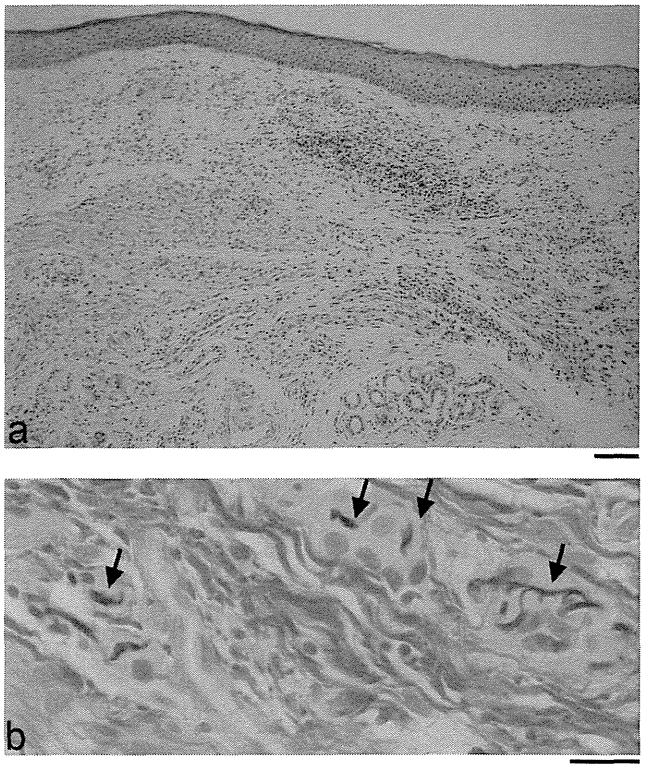


*Fig. 2.* Inflammatory cell infiltration and non-palisading granulomas in the upper to mid-dermis (haematoxylin and eosin) (a). Phagocytosis of elastic fibres by multinucleated giant cells and macrophages (Elastica van Gieson) (b). Arrows indicate elastic fibres in multinucleated cells and macrophages. Scale bars: 100 μm (a) and 20 μm (b).

## DISCUSSION

AEGCG is a rare, reactive granulomatous dermatosis, usually associated with actinic damage (1). The pathogenesis of AEGCG is unidentified. Both normal and degenerated elastic fibres are phagocytosed by macrophages in AEGCG (3). Several treatments for AEGCG have previously been proposed, including topical or intralesional glucocorticoids, cyclosporine, topical calcineurin inhibitors, dapsone, hydroxychloroquine sulphate, clofazimine, cryotherapy, methotrexate, psoralen plus ultraviolet A therapy, narrowband ultraviolet B therapy, retinoids, fumaric acid esters, and tranilast. However, most treatments are unsatisfactory, and there is no definitive therapy for AEGCG (5–7). A triple antibiotic therapy regimen, which included minocycline, has previously been reported to provide some beneficial effects for granuloma annulare (8), although not curing the disease (9). Minocycline has anti-inflammatory effects that interfere with lymphocyte proliferation, especially that of T cells, as well as immunomodulating and anti-granulomatous effects (10, 11). We considered that these mechanisms of action of minocycline may have affected AEGCG in the present patient. However, minocycline should be used with care, as it may be associated with photosensitivity. This could potentially worsen, rather than improve AEGCG, as previously reported with doxycycline (12).

To our knowledge, this is the first time that AEGCG was successfully treated with minocycline. In conclusion, the present case suggests that minocycline may be a useful therapeutic option for AEGCG. We cannot, however, exclude a spontaneous resolution of the lesion, and further case reports and studies are needed to confirm our observation.

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growth of the tissues supplied.[4] This may explain the appearance of granulomatous rosacea, a potentially immunologically mediated condition, in the location of prior nerve-related infection.[1,5]

In the case presented, 1 or more of the proposed mechanisms may have contributed to the development of an isotopic response. Further investigation of the immunologic, vascular, and neurologic changes after viral infection may clarify the link between primary herpes virus infection and the appearance of secondary dermatoses.

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*The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Navy, US Army, or the Department of Defense.*

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## Large epidermal cleft formation in verrucous-keratotic malignant melanoma of the heel

*To the Editor:* Verrucous-keratotic malignant melanoma is an uncommon clinical variant of malignant melanoma that can be confused with benign lesions. We report a verrucous-keratotic melanoma on the heel that we had difficulty diagnosing accurately at the first examination.

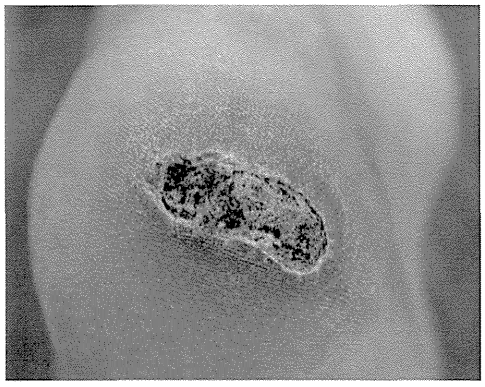

**Fig 1.** Verrucous-keratotic malignant melanoma. A verrucous hyperkeratotic plaque on the left heel, mimicking a plantar wart.

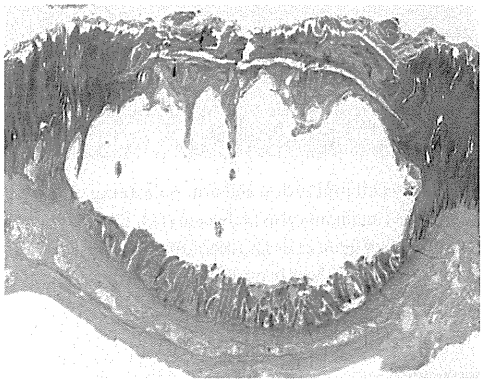

**Fig 2.** Verrucous-keratotic malignant melanoma. An extremely large cleft is seen at the center of the tumor.

A 65-year-old man came to our department with a pigmented hyperkeratotic lesion on his right heel. The blackish lesion had appeared a half-year before his first visit, and it had gradually enlarged.

Physical examination revealed a black, slightly elevated plaque 3.0 × 1.0 cm in size (Fig 1). The surface was ragged and covered with thick scales. Histopathologic examination of sample from shave biopsy revealed atypical melanocytes scattered throughout the horny layers. We totally excised the lesion with a wide margin. A histologic examination of the resected tumor showed prominent epidermal hyperplasia and elongated dermal papillae. Dissociation between melanoma cells in the basal layer and the suprabasal epidermis had caused a large cleft to form in the epidermis (Fig 2). Numerous atypical melanocytes were observed lining up in a row on the basement membrane.

We evaluated it as Clark level II, and sentinel lymph node biopsy was carried out. As a result, no metastasis was recognized in the sentinel lymph nodes.

Although verrucous-keratotic malignant melanoma is not included in the widely accepted

classification of Clark et al,[1] this case suggests that we should keep verrucous-keratotic malignant melanoma in mind as an important differential diagnosis for verrucous, hyperkeratotic lesions. In this case, the subtle perilesional clinical appearance of dark infiltration at the ridges might have been a clue to the diagnosis of melanoma.

The intercellular adhesion between melanoma cells is much weaker than that between normal keratinocytes, because melanocytes or melanoma cells do not have desmosomes. In addition, membranous expression of E-cadherin, which is responsible for melanocyte-keratinocyte adhesion, is sometimes decreased in melanoma progression.[2] Thinning of the epidermis with attenuation of the basal and suprabasal layers, described as "consumption of the epidermis," is frequently seen in areas of direct contact between the epidermis and melanoma cell nests.[3] Consumption of the epidermis occasionally results in the formation of a cleft separating the thin epidermis and melanoma cell nests.[3] Braun-Falco et al[4] reported that the clefts are a reliable diagnostic criterion for malignant melanoma. It has been suggested that the greater the Breslow depth, the greater the consumption of the epidermis in a melanoma lesion.[5] However, the Breslow depth of the current lesion did not appear to be very great, although we were unable to measure it accurately because of the large size of the cleft. The presence of the verrucous architecture may be associated with the presence of epidermal consumption. In the current case, melanoma cells completely replaced the basal layer keratinocytes, forming only a single-layer lining on the basement membrane. This characteristic infiltration pattern of melanoma cells with fragile cell adhesion might have lead to the large cleft with features mimicking the tombstone appearance of pemphigus vulgaris, although in the current lesion, the tombstones were melanoma cells instead of the basal keratinocyte tombstones of pemphigus vulgaris lesions.

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## Acral localized acquired cutis laxa: Report of a case associated with inflammatory arthritis

*To the Editor:* Acral localized acquired cutis laxa (ALACL) is a distinct variant of acquired cutis laxa characterized by loose redundant skin primarily confined to the distal extremities. It is often associated with signs or symptoms of a preceding inflammatory dermatosis, such as urticaria, erythema, swelling, or pruritus. Disease associations include multiple myeloma, idiopathic urticaria, Raynaud phenomenon, and rheumatoid arthritis. We report a case associated with inflammatory arthritis in childhood.

A 41-year-old woman with a history of polyarticular juvenile idiopathic arthritis diagnosed at age 3 presented with asymptomatic loose, pendulous skin confined to her volar finger pads and toes. She noted the onset of loose skin at age 6 and described ill-defined erythema, warmth, and pruritus of her hands that preceded the development of the skin changes. The degree of skin laxity remained stable since childhood. There was no history of urticaria. Family history was relevant for a paternal grandfather with rheumatoid arthritis.

On examination, there was loose redundant skin on the finger pads bilaterally that gave them a flat rounded appearance (Fig 1). The volar finger pads were soft on palpation and the skin remained depressed when pressure was applied, giving them an appearance that has been described as "chewing gum-like."[1] The plantar surface of the toes had similar skin changes, although less striking. Facial appearance was normal and did not show advanced aging.

present. The retrospective analysis of Surveillance, Epidemiology, and End Results database demonstrated head and neck area to be the predominant location of MAC (74%), followed by trunk (9%), upper extremities (8.5%), and lower extremities (5.4%). Only 2 cases (0.9%) involved the vulva (labia majora); whereas 0.9% were categorized as skin not otherwise specified, no penile involvement was reported.[1] Further, we could not identify reports of MAC in the penile region. Syringomatous carcinoma may be considered a variant of MAC and is characterized by ductal proliferation with a tadpole pattern, extension into subcutaneous tissue, and perineural involvement without follicular differentiation. Cellular atypia and mitoses may be observed.[2]

Although syringomas most commonly develop in the periorbital region, presentation with confluent plaquelike morphology is rare and was first described by Kikuchi et al[3] in 1979. To our knowledge, plaque-like syringoma on the penile shaft has only been described once.[4] Furthermore, although only 1 case of vulvar syringoma with subcutaneous extension has been previously described,[5] published cases of penile syringomas have been confined to the papillary and mid dermis.

Our rare case of plaquelike penile syringoma with extension of ductal structures to involve the reticular dermis is unusual and creates a potential for misdiagnosing this benign entity. However, consideration of clinical and histologic characteristics can help in distinguishing it from MAC/syringomatous carcinoma. In conclusion, adequate tissue sampling and clinical-pathological correlation are critical to avoid a potential diagnostic pitfall.

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## Urticaria pigmentosa complicated with esophageal eosinophilia

*To the Editor:* Mastocytosis is defined as an accumulation of clonal mast cells, and it may involve only the skin (urticaria pigmentosa, UP) or it may have a systemic presentation with multiorgan involvement. We report a patient with UP associated with esophageal eosinophilia.

A 20-year-old man was referred to our hospital with an 8-year history of itchy eruptions. He had intense itching after rubbing the lesions. He had had no episodes of diarrhea, abdominal pain, dysphagia, or gastroesophageal reflux disease (GERD)-like symptoms. Physical examination revealed multiple round brownish macules of less than 1 cm in diameter on the trunk and extremities (Fig 1). Darier sign was positive. Skin biopsy showed dense mast cell infiltrates in the dermis. They were CD117 (c-KIT) positive. Laboratory analyses showed a white blood cell count of 4600/$\mu$L, eosinophils at 6.6%, IgE at 737 IU/L, a total tryptase level of 2.2 $\mu$g/mL, and a histamine level of 1.52 ng/mL (normal range: 0.15 to 1.23).

To exclude systemic mastocytosis with multiorgan involvement, we performed computed tomography scans and endoscopic examinations. Upper gastrointestinal endoscopy revealed white linear furrows on the esophageal mucosa (Fig 2). Biopsy specimens from the esophageal mucosa showed dense eosinophilic infiltrates at more than 20 eosinophils per high-power field, and the specimens also contained sparsely infiltrating tryptase-positive mast cells. The infiltrating mast cells aberrantly expressed CD2. No activating germline KIT mutations were detected in the patient's peripheral blood cells. Under the diagnosis of UP complicated with esophageal eosinophilia, we have been following up the patient every half-year without medication.

Eosinophilic esophagitis (EoE) can be diagnosed based on clinical and histopathologic features.[1,2] Clinically, symptoms of esophageal dysfunction are characteristic of EoE. Histopathologically,

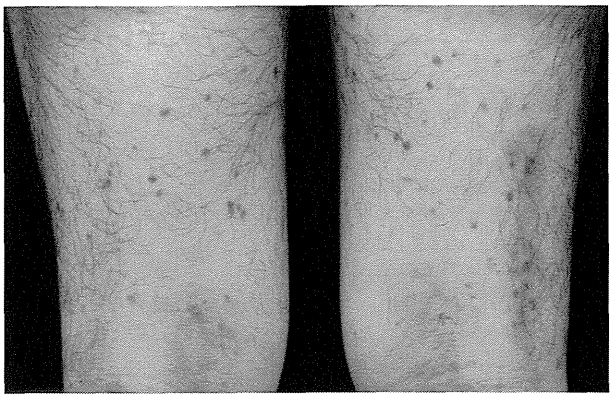

**Fig 1.** Urticaria pigmentosa. Multiple round brownish papules and macules on the legs.

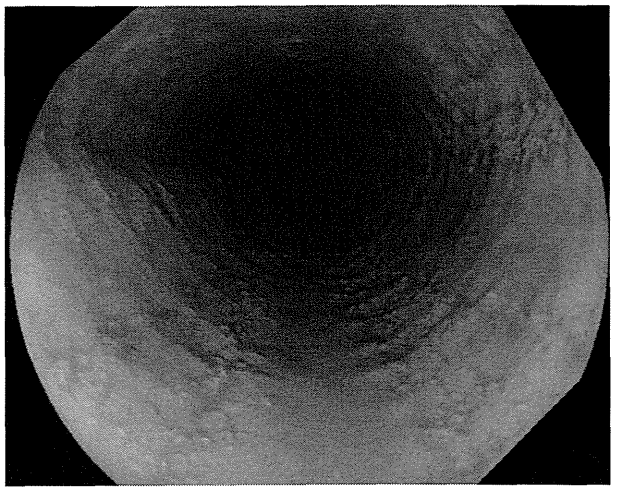

**Fig 2.** Esophageal eosinophilia. Concentric linear furrows on the esophageal mucosa.

eosinophil-predominant infiltration is seen in esophageal biopsy specimens.[1,2] Various conditions presenting esophageal eosinophilia, including GERD, should be excluded. The present case could not be diagnosed as EoE, because the patient had no apparent symptoms of esophageal dysfunction, although dense eosinophilic infiltration was seen in the esophageal biopsy specimens and the endoscopic features were consistent with EoE. The patient had no other disorders that might cause esophageal eosinophilia, and we cannot completely exclude the possibility that the patient's condition will progress to EoE in the future.

Chemical mediators released from mast cells are well known to induce eosinophilic infiltration. TGF-$\beta$1, which is expressed by both eosinophils and mast cells, has been recognized as an important molecular mediator of EoE.[3] Abonia et al[3] provided evidence for the involvement of KIT ligand in the pathogenesis of EoE. Niranjan et al[5] reported that mast cells play a critical role in muscular cell hyperplasia and possibly in the esophageal functional impairment of EoE. In this context, mast cell infiltration in the esophagus and/or the skin may have triggered the onset of esophageal eosinophilia in the present case, although the mast cell infiltration in the esophagus was sparse and the esophagus was not apparently involved in the mastocytosis. The present case might indicate an association between UP and esophageal eosinophilia.

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## Absence of HLA-DR1 positivity in 2 familial cases of frontal fibrosing alopecia

*To the Editor:* Frontal fibrosing alopecia (FFA) is a variant of lichen planopilaris (LPP), a specific presentation of lichen planus involving the hair follicles.[1,2] HLA-DR1 positivity has already been linked to cases of lichen planus and another variant

PLOS | GENETICS

# Revertant Mutation Releases Confined Lethal Mutation, Opening Pandora's Box: A Novel Genetic Pathogenesis

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## Abstract

When two mutations, one dominant pathogenic and the other "confining" nonsense, coexist in the same allele, theoretically, reversion of the latter may elicit a disease, like the opening of Pandora's box. However, cases of this hypothetical pathogenic mechanism have never been reported. We describe a lethal form of keratitis-ichthyosis-deafness (KID) syndrome caused by the reversion of the *GJB2* nonsense mutation p.Tyr136X that would otherwise have confined the effect of another dominant lethal mutation, p.Gly45Glu, in the same allele. The patient's mother had the identical misssense mutation which was confined by the nonsense mutation. The biological relationship between the parents and the child was confirmed by genotyping of 15 short tandem repeat loci. Haplotype analysis using 40 SNPs spanning the >39 kbp region surrounding the *GJB2* gene and an extended SNP microarray analysis spanning 83,483 SNPs throughout chromosome 13 in the family showed that an allelic recombination event involving the maternal allele carrying the mutations generated the pathogenic allele unique to the patient, although the possibility of coincidental accumulation of spontaneous point mutations cannot be completely excluded. Previous reports and our mutation screening support that p.Gly45Glu is in complete linkage disequilibrium with p.Tyr136X in the Japanese population. Estimated from statisitics in the literature, there may be approximately 11,000 p.Gly45Glu carriers in the Japanese population who have this second-site confining mutation, which acts as natural genetic protection from the lethal disease. The reversion-triggered onset of the disesase shown in this study is a previously unreported genetic pathogenesis based on Mendelian inheritance.

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**Competing Interests:** The authors have declared that no competing interests exist.

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## Introduction

A nonsense mutation may, in theory, disrupt and thus "confine" the effects of another dominant pathogenic mutation when the two mutations coexist in the same allele of a single gene. Furthermore, in such cases, reversion of the confining nonsense mutation may paradoxically elicit a congenital disease, although proven cases of this hypothetical pathogenesis have not been reported.

Keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210) is a rare congenital ectodermal disorder characterized by vascularizing keratitis, ichthyosiform erythroderma and sensorineural hearing loss [1]. KID syndrome is mainly caused by a heterozygous germ line missense mutation in GJB2 (Entrez Gene ID: 2706) encoding connexin 26 (Cx26) (RefSeq: NM_004004.5) [2–4].

Here we report a case of KID syndrome where the reversion of a missense mutation induced a lethal disease. We encountered a girl with KID syndrome from obviously healthy parents, and sequence analysis of *GJB2* revealed a heterozygous missense mutation, p.Gly45Glu, in the patient. Unexpectedly, her healthy mother also had the heterozygous missense mutation p.Gly45Glu, as well as another heterozygous nonsense mutation: p.Tyr136X. From these findings, we hypothesized that the p.Tyr136X mutation confines the pathogenic effect of p.Gly45Glu in the mother and that the reversion of p.Tyr136X triggered the onset of KID syndrome in the patient. In the present study, TA cloning and haplotype analysis of the family confirmed that an allelic recombination event involving the maternal allele carrying the two mutations generated the pathogenic allele unique to the patient. Furthermore, cotransfection experiments and a neurobiotin uptake assay clearly demonstrated that the p.Tyr136X mutation confines the pathogenic effects of the p.Gly45Glu mutation. Thus, to our knowledge, the present findings provide the first evidence of reversion-triggered onset of a congenital disease.

## Results

### The Patient's Mother Had Both *GJB2* Lethal Missense Mutation and Confining Nonsense Mutation, Although the Patient Had Only the Lethal One

The KID syndrome patient is a girl born from apparently healthy Japanese parents. She showed ichthyosiform erythroderma

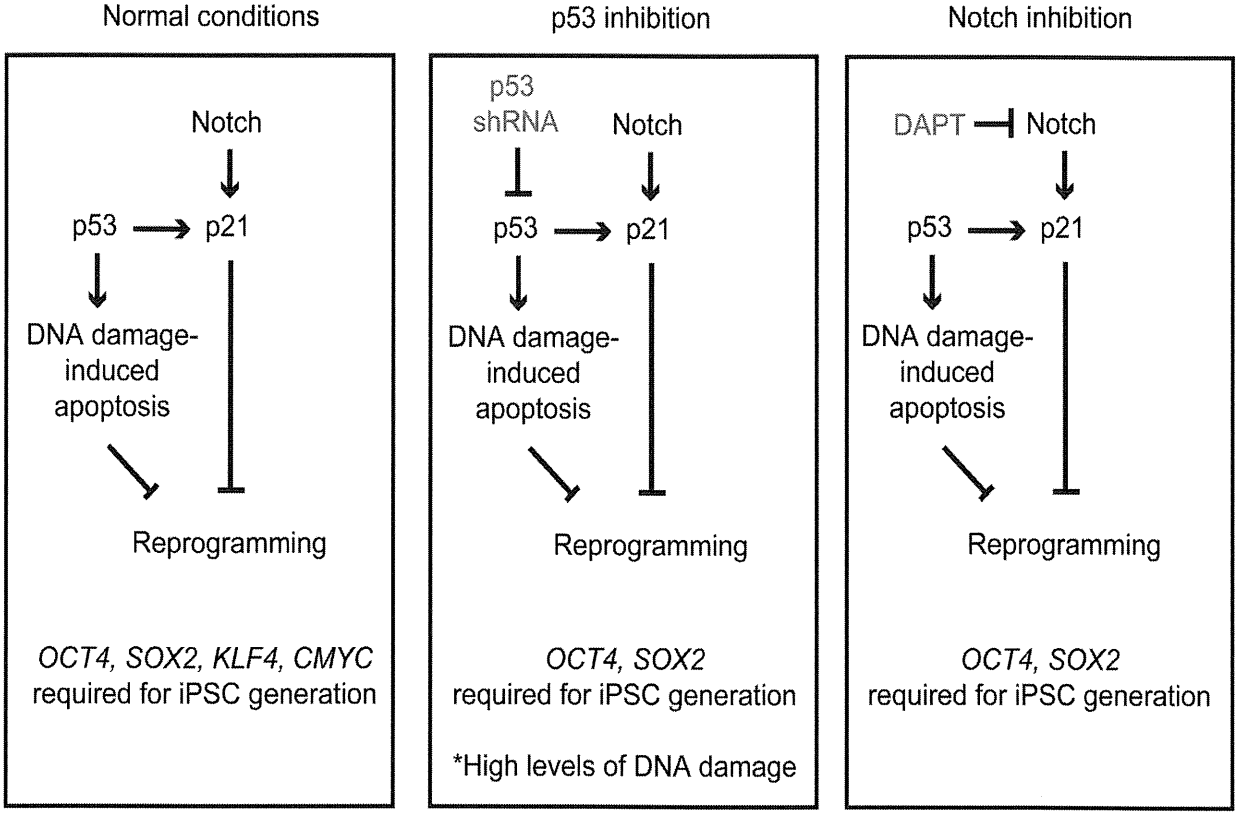


**Figure 6. Model of iPSC generation from human keratinocytes**

Notch inhibition allows the production of safer oncogene-free iPSCs by suppressing p21 in a p53-independent manner.