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CARD14 – Associated Papulosquamous Eruption (CAPE): A Spectrum Including Features of Psoriasis and Pityriasis Rubra Pilaris

Brittany G. Craiglow, MD[1,*], **Lynn M. Boyden, PhD**[2,*], **Ronghua Hu, MD**[1], **Marie Virtanen, MD**[5], **John Su, MD**[6,7], **Gabriela Rodriguez**[8], **Catherine McCarthy, MD, PhD**[9], **Paula Luna, MD**[10], **Margarita Larralde, MD, PhD**[10], **Stephen Humphrey, MD**[11], **Kristen E. Holland, MD**[11], **Marcia Hogeling, MD**[12], **Benjamin Hidalgo-Matlock, MD**[8], **Bruno Ferrari, MD**[10], **Esteban Fernandez-Faith, MD**[13,14], **Beth Drolet, MD**[11], **Kelly M. Cordoro, MD**[15,16], **Anne M. Bowcock, PhD**[17,18,19], **Richard J. Antaya, MD**[1,3], **Kurt Ashack, MD**[20], **Richard J. Ashack, MD**[21], **Richard P. Lifton, MD, PhD**[2], **Leonard M. Milstone, MD**[1,^], **Amy S. Paller, MD**[22,23,^], and **Keith A. Choate, MD, PhD**[1,2,4]

[1]Department of Dermatology, Yale University School of Medicine, New Haven, CT

[2]Department of Genetics, Yale University School of Medicine, New Haven, CT

[3]Department of Pediatrics, Yale University School of Medicine, New Haven, CT

[4]Department of Pathology, Yale University School of Medicine, New Haven, CT

[5]Department of Dermatology, Uppsala University Hospital, Uppsala, Sweden

[6]Department of Dermatology, Monash University, Eastern Health, Melbourne, Australia

[7]Department of Pediatrics, Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia

[8]Department of Dermatology, University of Costa Rica, San Jose, Costa Rica

[9]Department of Medicine, Washinton University School of Medicine, Saint Louis, Missouri

[10]Department of Pediatric Dermatology, Ramos Mejía Hospital, Buenos Aires, Argentina

[11]Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin

[12]Division of Dermatology, David Geffen School of Medicine at University of California, Los Angeles, CA

[13]Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University Medical Center

Correspondence: Keith Choate, Department of Dermatology, Yale University School of Medicine, PO Box 208059, New Haven, Connecticut 06520, USA or keith.choate@yale.edu.

*These authors contributed equally to this work.

^These authors also contributed equally.

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[14]Department of Dermatology, Nationwide Children's Hospital and The Ohio State University Medical Center

[15]Department of Dermatology, University of California, San Francisco, San Francisco, CA

[16]Department of Pediatrics, University of California, San Francisco, San Francisco, CA

[17]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

[18]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

[19]Department of Genetics & Genome Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

[20]Department of Dermatology, University of Illinois at Chicago College of Medicine, Chicago, Illinois

[21]Dermatology Associates of West Michigan, Grand Rapids, Michigan

[22]Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL

[23]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Background—Heterozygous mutations in *CARD14* have been shown to be associated with psoriasis and familial pityriasis rubra pilaris (PRP). Many patients with *CARD14* mutations display features of both disorders, which can result in diagnostic uncertainty. In addition, these eruptions are often recalcitrant to conventional psoriasis therapies such as methotrexate, oral retinoids and TNF-α inhibitors.

Objective—We sought to describe the clinical characteristics, family history, and response to therapy in subjects with papulosquamous eruptions due to mutations in *CARD14*.

Methods—Subjects were referred for genetic testing as part of a registry of patients with inherited disorders of keratinization. DNA was isolated from blood or saliva, and multiplex targeted next generation sequencing or whole exome sequencing was performed. Clinical histories of subjects with *CARD14* mutations were reviewed.

Results—We identified 15 kindreds with *CARD14*-associated papulosquamous eruption (CAPE). Characteristic features of CAPE include early age of onset, prominent involvement of the cheeks, chin and ears, family history of psoriasis or PRP, minimal response to conventional topical and systemic psoriasis therapies, and improvement with ustekinumab.

Limitations—Relatively small sample size.

Conclusions—Many subjects with *CARD14* mutations display characteristics of both psoriasis and PRP. We propose the term *CARD14*-associated papulosquamous eruption (CAPE) to describe this spectrum of disease. Patients with clinical features suggestive of CAPE should undergo *CARD14* sequencing and may benefit from treatment with ustekinumab.

Introduction

Psoriasis and pityriasis rubra pilaris (PRP) have traditionally been considered distinct entities with overlapping therapeutic choices. Heterozygosity for mutation in *CARD14* (MIM 697211), which encodes caspase recruitment domain family member 14,[1] has been independently reported to be associated with familial and nonfamilial forms of psoriasis, including pustular psoriasis and psoriasis associated with arthritis,[2,3] as well as familial PRP,[4] indicating that these disorders share a common underlying pathophysiology. We describe 15 families with mutations in *CARD14*, members of which display a range of clinical findings that include features of both psoriasis and PRP. We propose the term *CARD14*-associated papulosquamous eruption (CAPE) to describe this spectrum of disease. We include the first observation of homozygosity for a pathogenic *CARD14* mutation in a subject with a severe phenotype and describe six subjects who responded favorably to treatment with ustekinumab after failure to respond to other therapies.

Methods

The study was approved by the Yale Human Investigational Committee and complies with the Declaration of Helsinki Principles. Subjects were referred by dermatologists from a variety of institutions for participation in a genetic study of inherited disorders of keratinization, many with a suspected diagnosis of PRP. Individual consent or parental permission was obtained in writing for each case. DNA was isolated from peripheral blood or saliva of the index case in each kindred, and either exome sequencing, GeneRead targeted sequencing, or Sanger sequencing was performed as previously described.[5] The medical records of subjects demonstrating *CARD14* mutations were reviewed.

Results

Fifteen kindreds with *CARD14* mutations were identified, and clinical features of the index cases are presented in detail in the Table. With the exception of 2 subjects, all had onset of their disease at or before one year of age. The skin phenotype ranged from predominantly psoriasis-like to predominantly PRP-like, with several patients showing features typical of both diseases. Two patients were erythrodermic. The most notable characteristic among the group is prominent facial involvement, which was displayed by all but 1 subject and in most cases presented early in the disease course as symmetric, well-demarcated pink-red patches or thin plaques involving the bilateral cheeks and chin with sparing of the infralabial region (Figure 1). Many also had erythema of the ears. Involvement of the trunk and extremities was more variable, ranging from scattered pink, scaly plaques to confluent erythema and scale (Figures 2A–D). One patient showed striking patterned plaques on the chest and back (Figure 2C), and two patients did not have any truncal involvement. Five subjects displayed classic ‘islands of sparing,’ and 6 showed follicular papules that are typical of PRP. Most (12/15) subjects had some degree of palmoplantar keratoderma, and two had scleroderma-like changes of the hands.

The patients have been treated with a number of modalities with varying degrees of success. None has experienced remission of disease without treatment. Response to topical

medications, including corticosteroids, calcineurin inhibitors, Vitamin D analogues, topical retinoids, and tar preparations had been universally minimal among the group. Responses to other treatments, including phototherapy, oral retinoids, methotrexate, cyclosporine and biological therapies had been variable and are detailed in the Table. Among the eight subjects who had been treated with etanercept as monotherapy, only one subject demonstrated partial response, six had minimal response, and one had worsening. Notable is the near complete response to ustekinumab in 5 of 6 subjects treated and partial response in the sixth (subject 5), who had the most severe phenotype and was also notably the heaviest and thus may have required a higher dosage. Indeed, subject 9 required 90 mg (1.2 mg/kg) dosed every 8 weeks to maintain near complete clearance (Figure 3). He has recently been transitioned to guselkumab in the hopes that it might yield similar improvement but at the standard dosing regimen. Doses for the other patients treated with ustekinumab range from 0.7 mg/kg (in addition to methotrexate) to 1.1 mg/kg every 12 weeks.

Discussion

CARD14 mutations are independently associated with psoriasis[2,3] and familial PRP[4], providing a pathophysiologic link between these disorders. The subjects in this series provide striking clinical evidence for this connection and display findings characteristic of both PRP and psoriasis. While all of the subjects have some features consistent with PRP, their presentations do not fit squarely within the traditional PRP classification.[6] The early age of onset and chronicity of disease are consistent with atypical juvenile PRP, but many subjects do not display the typical keratotic papules and only two show scleroderma-like changes of the hands. In addition, a few subjects demonstrate the typical ‘islands of sparing’ characteristic of classic adult and juvenile PRP, but others show generalized scaly plaques that are more reminiscent of extensive plaque psoriasis. Three subjects have arthritis, which is reported in approximately 5–30% of patients with psoriasis,[7–9] but is uncommonly associated with PRP.[10,11] These varying phenotypes support the requirement for other environmental and genetic factors beyond the *CARD14* mutation in determining clinical manifestations and disease severity.

With the exception of p.Q157P, all of the *CARD14* mutations in our subjects have either been previously reported or change the same nucleotide as previously reported mutations[3,4,12–16]. Repeated occurrence of mutations at a small number of clustered sites in unrelated families, many of which arose *de novo*, provides further evidence of the critical importance of these specific residues to *CARD14* function and pathobiology. Notably, we report the first observation of homozygosity for a rare pathological mutation in *CARD14*. While this subject’s phenotype is more severe than her heterozygous relatives, it is not the most severe in our cohort, nor are any unique features apparent. This suggests there is relatively little dosage effect for the p.G117S mutation.

CARD14 functions as an activator of NF-κB signaling,[1,17] and NF-κB has been shown to be upregulated in the skin of patients with PRP and *CARD14* mutations.[4] Elevated NF-κB activity leads to increases in chemokines such as IL-8 and CCL20, which lead to recruitment and differentiation of inflammatory cells, including production of IL-23 by dendritic cells and IL-17 and IL-22 by T cells.[3] As an inhibitor that targets both IL-12 and IL-23 cytokines

by binding to their shared p40 subunit[18,19], ustekinumab is a pathogenesis-based treatment for CAPE, as demonstrated by the marked clinical response in 5 of 6 subjects treated with ustekinumab in our series. Given his weight, we speculate that the sixth subject might have demonstrated greater improvement had he received a higher dose, as lower serum ustekinumab concentrations and decreased efficacy have been recorded in psoriasis patients with higher weights,[20] and others in this series received higher doses and/or more frequent administration. PRP is often difficult to treat, but ustekinumab has also successfully treated adult-onset PRP in several case reports[21–26] and recently in two patients with familial PRP associated with *CARD14* mutation.[12,16] Guselkumab, an IL-23p19 inhibitor, recently approved for the treatment of plaque psoriasis, represents another potential pathogenesis-based treatment for this group of patients, as do secukinumab, an IL-17A inhibitor, and ixekizumab, an IL-17 inhibitor. Notably, however, the one subject in this series treated with ixekizumab only had a partial response.

The possibility of *CARD14* mutation should be considered in patients with papulosquamous eruptions characterized by features of both psoriasis and PRP, especially those who present with early onset of disease, facial involvement, and family history of psoriasis or PRP. While individually these characteristics are not specific, the constellation of findings are highly suggestive of CAPE, particularly when coupled with inadequate response to conventional psoriasis therapies such as methotrexate, acitretin or TNF-α inhibitors. Our experience positions ustekinumab as the preferred treatment for this group of patients; however, higher than standard dosing and/or more frequent dosing may be necessary to maintain improvement. Based on the pathogenesis of CAPE, guselkumab, secukinumab and ixekizumab may also be effective and therefore warrant further exploration. While we expect that over time we will learn more about the range of clinical features associated with CAPE, we hope that our experience with this group of patients will help to identify and successfully treat affected individuals.

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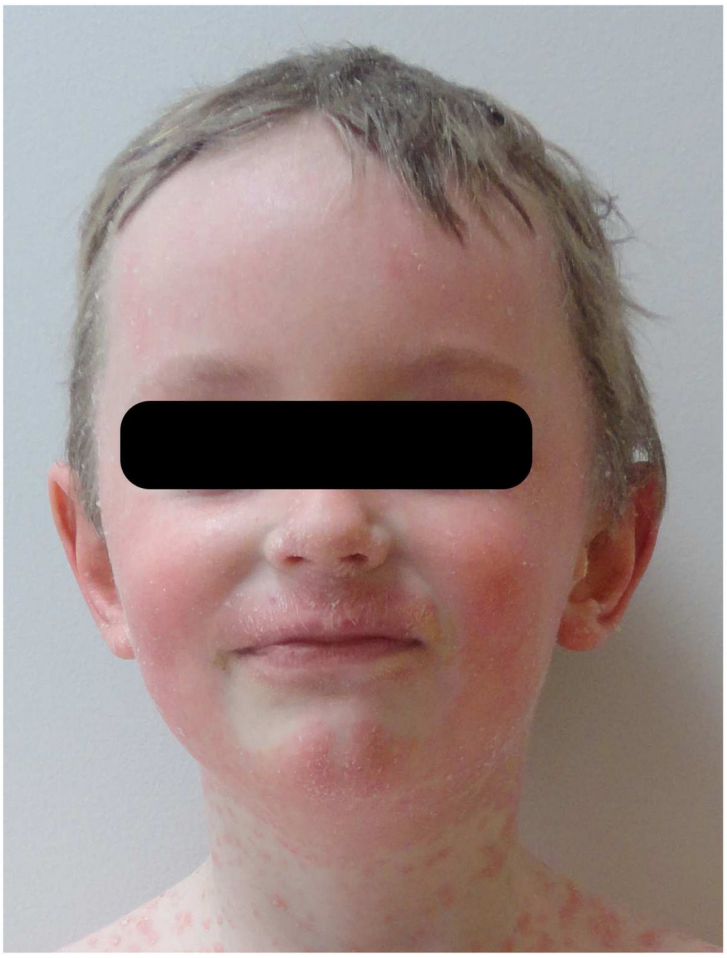
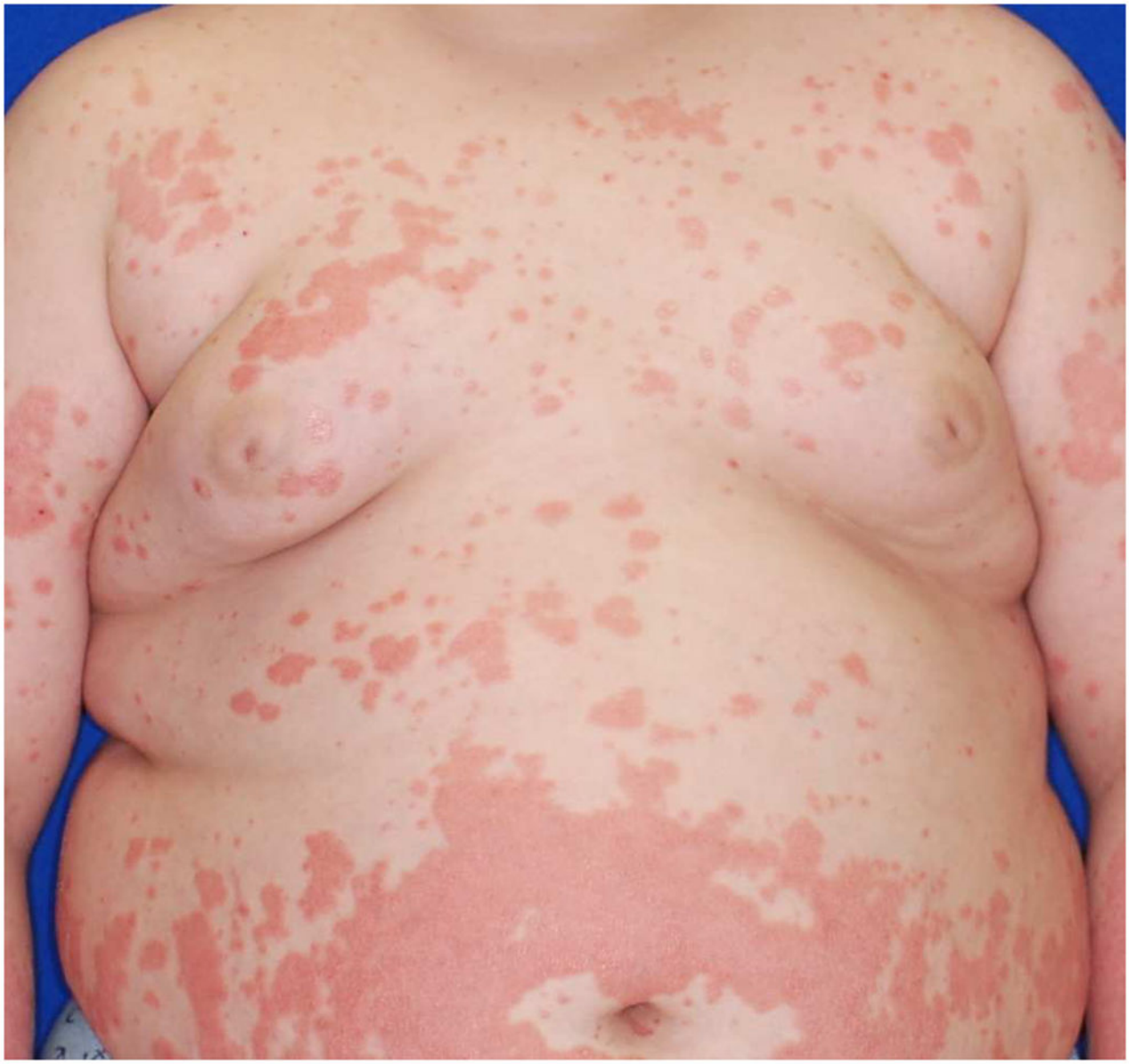
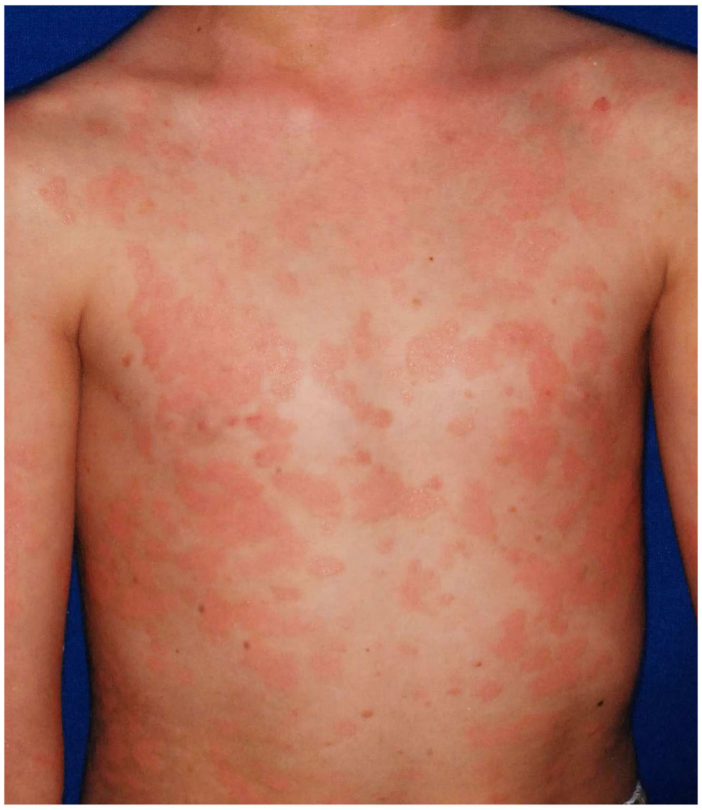
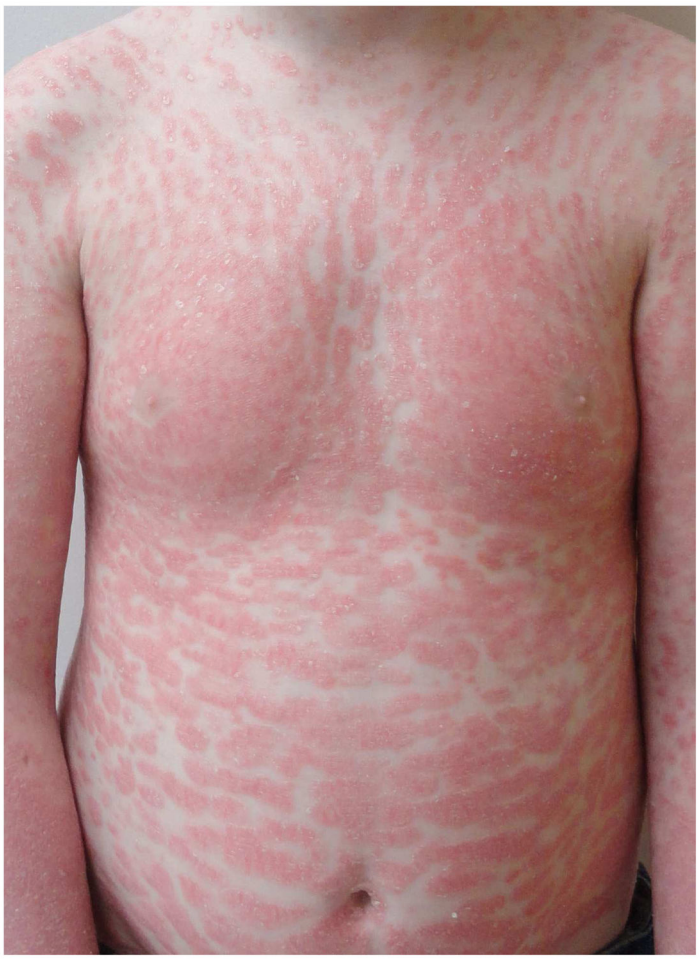


Figure 1. Characteristic facial involvement in CAPE

Symmetric and geometric pink, scaly patches or plaques involving the cheeks, upper cutaneous lip and chin with sparing of the infralabial region is highly characteristic of CAPE.







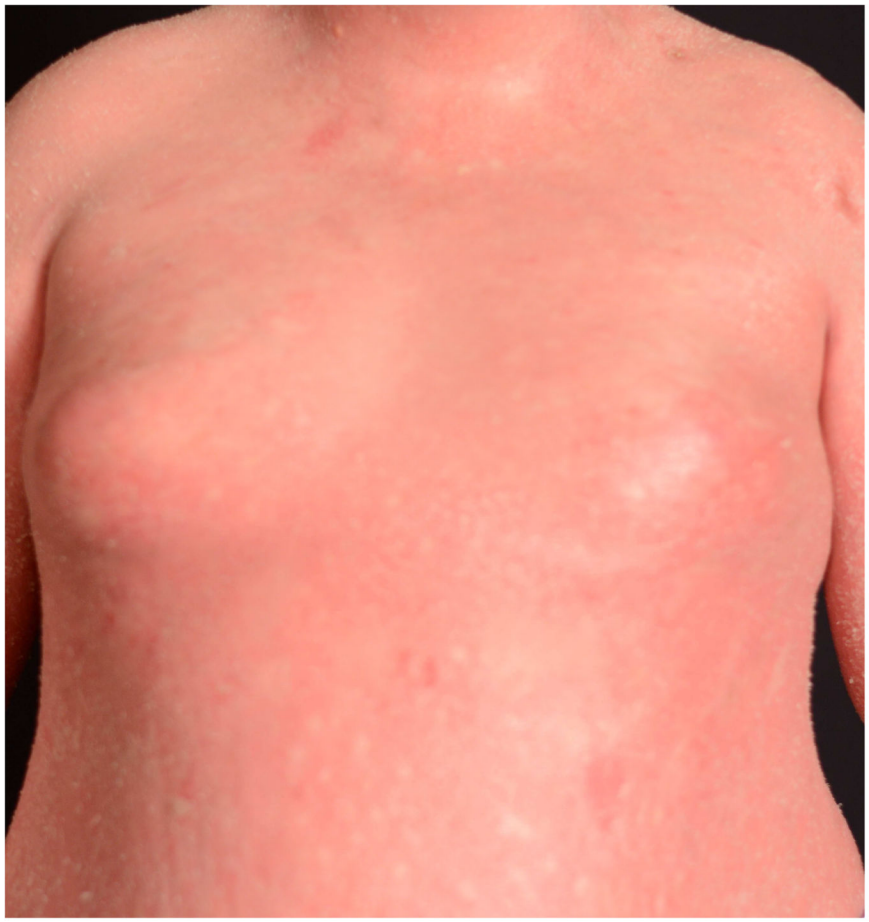
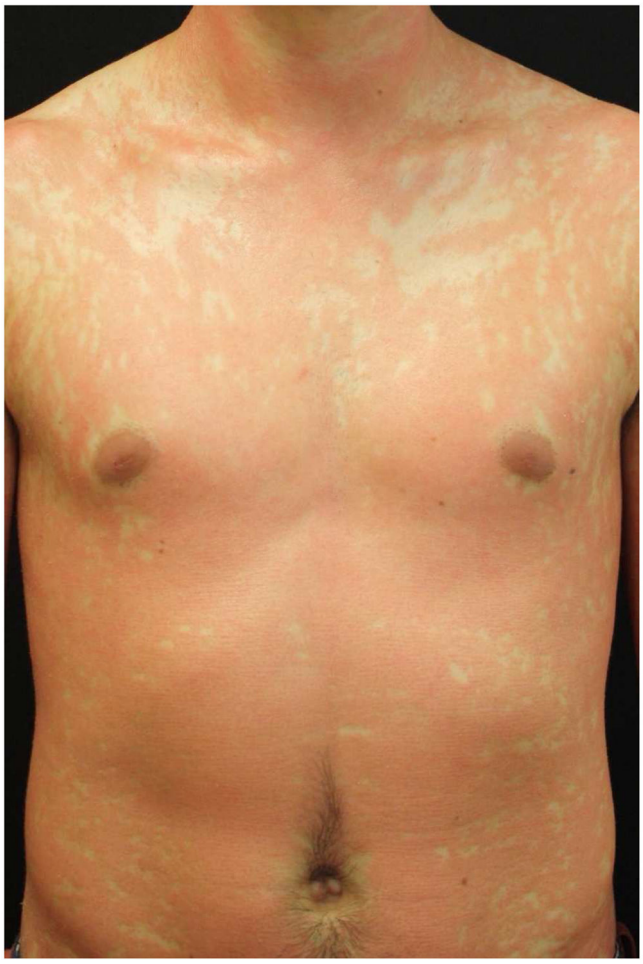


Figure 2. Spectrum of phenotypes of patients with CAPE

Clinical appearance ranges from more psoriasis-like (a), mixed features of psoriasis and PRP (b), to PRP-like (c), to erythroderma (d).



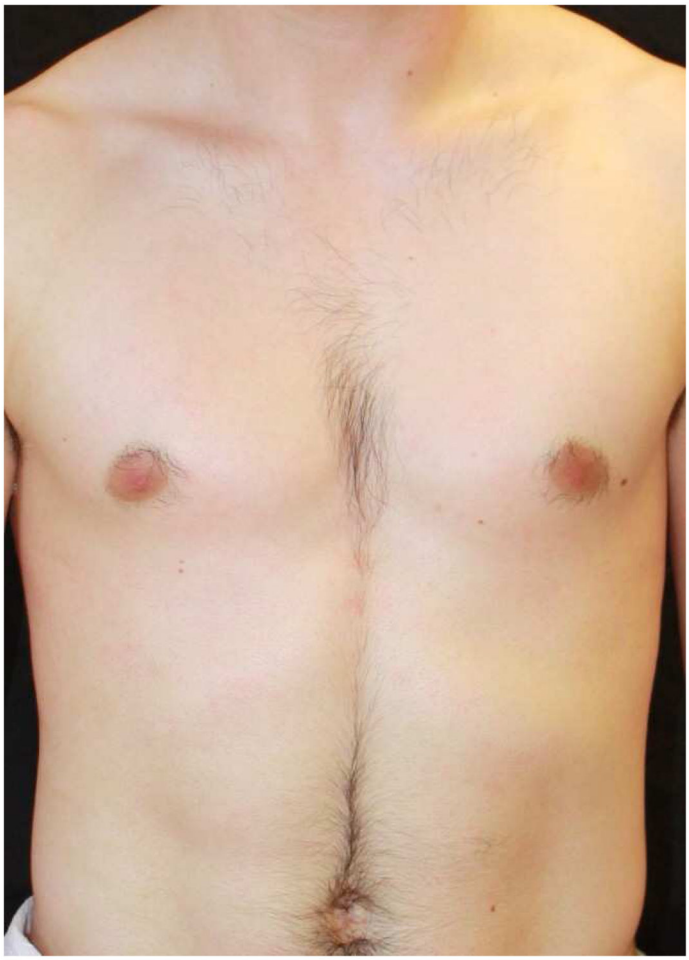


Figure 3. Response to ustekinumab

Subject 9 at baseline demonstrating widespread thin pink plaques with classic ‘islands of sparing’ (a) and after 6 months of treatment with ustekinumab (b). He demonstrated near complete clearance after 2 monthly doses of 0.6 mg/kg but in order to maintain this he ultimately required ustekinumab 1.2 mg/kg every 8 weeks.

Table

Clinical characteristics of index cases and response to therapy

Subject	Mutation	Age of onset	Facial involvement	Classic 'Islands of	Follicular Papules	PPK	Additional Features	Treatment	Response	Family History
1	c.349G>A, p.G117S (homozygous)	8 months	yes	no	yes	yes	arthritis	1. NBUVB	1. partial	mother* with extensive plaque psoriasis; father* with subtle palmar hyperkeratosis; paternal uncle* with mild psoriasis (all heterozygous)
								2. isotretinoin	2. partial; near complete at 3–4 mg/kg/day	
								3. MTX	3. near complete	
								4. MTX + etanercept	4. near complete	
								5. MTX + ustekinumab 0.7mg/kg q12 weeks	5. near complete	
2	c.380G>C, p.C127S	8 years	yes	yes	no	yes	arthritis, pustules	1. MTX	1. partial	brother*, mother*, & maternal GM* similarly affected
								2. etanercept	2. partial	
3	c.349+5G>C	2 years	yes	no	no	yes	none	1. MTX	1. minimal	paternal GF#, 2 paternal aunts#, 2 paternal cousins# with psoriasis
								2. isotretinoin	2. partial	
								3. etanercept	3. minimal	
								4. ustekinumab 1.1 mg/kg q12 weeks	4. near complete	
4	c.356T>G, p.M119R (de novo)	6 months	yes	no	no	no	none	1. acitretin	1. minimal	none
								2. etanercept	2. partial	
5	c.412G>A, p.E138K (de novo)	3 weeks	yes	no	no	yes	arthritis, contractures, ectropion	1. acitretin	1. minimal	none
								2. ustekinumab 0.87 mg/kg q12 weeks	2. partial	
6	c.349G>A, p.G117S	4 months	yes	yes	yes	yes	none	1. NBUVB	1. partial	father*, paternal GF* with mild psoriasis
								2. acitretin	2. partial	
7	c.467T>C, p.L156P	6 months	yes	yes	no	yes	none	1. adalimumab	1. minimal	father#, paternal GF#, 2 paternal aunts# and paternal cousin# similarly affected but to lesser degree
								2. ustekinumab 1.2mg/kg q8 weeks	2. near complete	
								3. ixekizumab	3. partial	
								4. guselkumab	4. pending	
8	c.349G>A, p.G117S	7 months	yes	no	no	no	truncal sparing	1. etanercept	1. minimal	father# with psoriasis
								2. NBUVB	2. partial	

Subject	Mutation	Age of onset	Facial involvement	Classic 'Islands of	Follicular Papules	PPK	Additional Features	Treatment	Response	Family History
								3. MTX	3. partial	
9	c.349G>A, p.G117S	1 year	yes	yes	no	no	none	1. etanercept	1. minimal	father *, paternal uncle, paternal GM, paternal great GF similarly affected
								2. MTX	2. partial	
								3. isotretinoin	3. partial	
								4. ustekinumab 0.87 mg/kg q12 weeks	4. near complete	
10	c.371T>C, p.L124P (de novo)	3 months	yes	yes	yes	yes	tapering of digits	1. MTX	1. minimal	none
								2. acitretin	2. partial	
								3. cyclosporine	3. partial	
								4. etanercept	4. worsening	
								5. PUVA	5. worsening	
								6. ustekinumab 0.9 mg/kg q12 weeks	6. near complete	
11	c.356T>C, p.M119T	1 month	yes	no	yes	yes	none	1. MTX	1. partial	father * similarly affected
								2. cyclosporine	2. partial	
								3. etanercept	3. minimal	
								4. MTX + PUVA	4. partial	
12	c.356T>C, p.M119T	1 year	no	no	yes	yes	none	1. acitretin	1. worsening	none
13	c.349G>A, p.G117S	6 months	yes	no	yes	yes	none	1. MTX	1. minimal	none
								2. etanercept	2. minimal	
14	c.349G>A, p.G117S	6 months	yes	no	no	yes	none	1. NBUVB	1. partial	mother * with psoriasis post-partum that resolved, maternal GF # with psoriasis, maternal aunt # with self-limited PRP
15	c.470A>C, Q157P	1 month	yes	no	no	yes	truncal sparing	1. MTX	1. partial	father # and several paternal cousins #
								2. isotretinoin	2. minimal	

* DNA of family member sequenced and shares mutation

DNA of family member not evaluated

Mutation nomenclature: c refers to the position of the mutation within the mRNA; p indicates the specific amino acid residue that is mutated

Abbreviations: PPK – palmoplantar keratoderma; hom – homozygous; MTX – methotrexate; GM – grandmother; GF - grandfather