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Correspondence

Aberrant CARD14 function might cause defective barrier formation

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Short title: Skin barrier defects and *CARD14* mutations

Abbreviations: CARD14, caspase recruitment domain family member 14; AD, atopic dermatitis; PRP, pityriasis rubra pilaris

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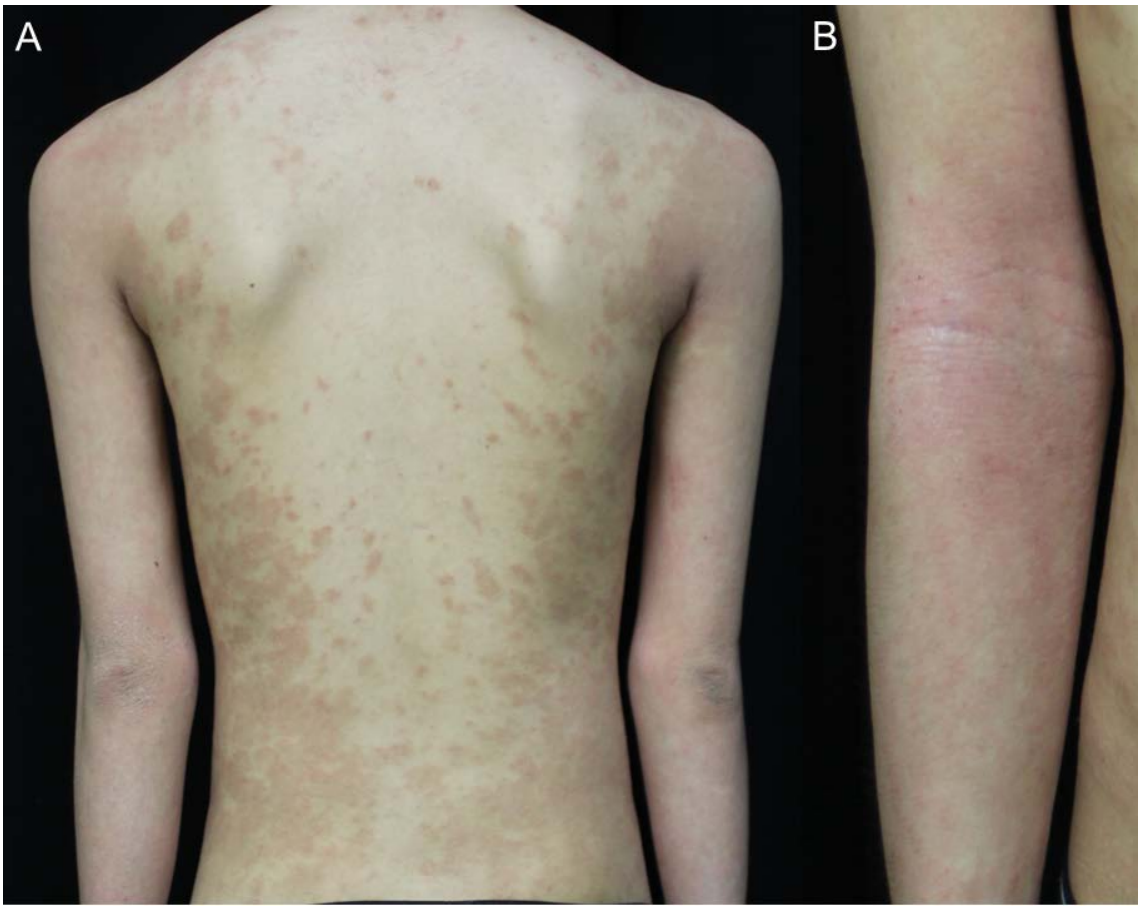
To the editor:

We read with great interest the recent report by Peled *et al*. on how loss-of-function mutations in *CARD14* (caspase recruitment domain family, member 14) are associated with a severe variant of atopic dermatitis (AD).[1] *CARD14* encodes a known regulator of nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB), and dominant gain-of-function mutations in *CARD14* cause psoriasis and related disorders.[1,2] Peled *et al*. revealed that dominant negative mutations in *CARD14* result in severe atopic dermatitis and decreased NF-κB signaling.[1] Their findings expand the spectrum of CARD14-associated phenotypes and shed light on the partially overlapping but also distinct pathophysiologic mechanisms underlying AD and psoriasis. We previously proposed that pityriasis rubra pilaris (PRP) type V, the atypical juvenile type, is a distinct variant of PRP that is caused by *CARD14* mutations.[3] We had a unique case of PRP type V who showed eczematous lesions and high serum IgE and thymus and activation-regulated chemokine (TARC), which suggested defective barrier function. Our findings indicate that the pathogenesis of AD with *CARD14* mutations might involve not only an imbalance of NF-κB/antimicrobial peptides, but also defective skin barrier function.

A 14-year-old boy was referred to our hospital with chronic erythematous hyperkeratotic lesions on the trunk and extremities. Erythema with scales was noticed in the extremities at birth, and the eruptions spread to the whole body. Physical examination revealed diffuse symmetrical erythematous hyperkeratotic eruptions on the upper extremities and the trunk, and moderate palmoplantar keratoderma (Fig. 1a). Notably, scratched eczematous lesions were seen on both elbows (Fig. 1b). He had hyperkeratosis on the palms and the soles. The laboratory test results of the patient were as follows: white blood cell count 6,700/mm^3 (normal range: 3800-8500/mm^3) with

11% eosinophils (normal range: 1-6%), interleukin (IL)-1β <10 pg/ml (normal range: <10 pg/ml), IL-18, 205 pg/ml (mean+1.78 SD), IgE 839 IU/mL (normal range: <233 IU/mL), and TARC level 1,384 pg/mL (normal range: <450 pg/mL). Whole-exome sequencing revealed a previously reported heterozygous gain-of-function variant, c.526G>C (p.Asp176His), in *CARD14*. We did not identify potentially pathogenic mutations/variants in any other genes implicated in inflammatory keratinization disorders or AD. We diagnosed him with type V PRP based on the clinical characteristics and the results of molecular analysis by whole-exome sequencing.



AD is considered to be caused by a combination of immunological abnormalities and epidermal barrier defects.[1] Our previously reported cases of PRP type V showed fine, scaly, diffuse erythema on the face, trunk and extremities, mimicking phenotypes of ichthyosis with skin barrier defects.[3,5] In the present patient, multiple eczematous lesions and laboratory data of AD (moderately elevated IgE and TARC)

were observed. Thus, our findings suggest that barrier dysfunction due to aberrant CARD14 function as well as the imbalance of NF-κB /antimicrobial peptides may be involved in the pathogenesis of AD associated with *CARD14* mutations. Further accumulation of AD cases or PRP cases with eczematous lesions associated with loss-of-function or gain-of-function *CARD14* mutations, respectively, is needed to confirm the involvement of barrier defects in the pathogenesis of their eczema.

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Figure legend

Figure 1. Clinical features of the present PRP patient with a *CARD14* gain-of-function variant.

(A) Diffuse symmetrical erythematous hyperkeratotic eruptions are seen in the upper extremities and on the back. (B) Scratched eczematous lesions are seen on the flexor side of the right elbow.