

## News Release

### Title

**Pityriasis rubra pilaris type V as an autoinflammatory disease by *CARD14* mutations**

### Key Points

○ We found *CARD14* mutations in all three pityriasis rubra pilaris (PRP) type V patients examined, but not in 19 PRP patients with other types.

○ Our findings suggest that type V PRP, both familial and sporadic, can be caused by *CARD14* mutations.

○ Detailed clinical observation revealed that all three patients displayed unique patchy macular brown hyperpigmentation.

### Summary

Prof. Masashi Akiyama, Dr. Takuya Takeichi (first author) at Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) and Prof. Kazumitsu Sugiura (corresponding author) at Department of Dermatology, Fujita Health University School of Medicine proposed a pityriasis rubra pilaris (PRP) type V as an autoinflammatory disease by *CARD14*, which encodes caspase recruitment domain family member 14 (*CARD14*), mutations.

PRP is one of the inflammatory keratinization disorders, which is characterized by scaly hyperkeratotic follicular inflammatory papules on extensor surface of the extremities and trunk. PRP is classified into six subgroups, types I to VI, based on clinical criteria (age of onset, distribution of lesions, disease course and presence/absence of HIV infection). PRP type V is an atypical juvenile type and the disease appears in the first few years of life. The patients show a chronic course. Recently, gain-of-function mutations in *CARD14* were identified in some autosomal dominant familial cases of PRP.

*CARD14* is an activator of nuclear factor kappa-light-chain-enhancer in activated B cells (NFκB) and contributes to inflammatory responses within the epidermis. Subsequent reports have also implicated *CARD14* variants in various autoinflammatory skin disorders, although the pathogenic relevance in each disease has not been well determined. To further determine how often PRP patients have pathogenic mutations in *CARD14* and to elucidate which clinical subtype of PRP is caused by *CARD14* mutations.

We sequenced the entire coding regions of *CARD14* in genomic DNA from 22 patients with five clinical subtypes of PRP. Among three PRP type V patients examined, all were found to have *CARD14* mutations. All three patients displayed unique patchy macular brown hyperpigmentation additionally to other typical features of PRP. Patients with PRP type I and type IV, one patient each, had the rare variants in *CARD14*.

The present study clearly demonstrated that PRP type V is a distinct variant of PRP that is

caused by *CARD14* mutations. In addition, a rare variant of *CARD14* might also be implicated in the pathophysiology of other forms of PRP. Our data suggest that anti-inflammatory therapy targeting *CARD14* may be a promising therapeutic strategy for autoimmune diseases such as PRP type V.

## Research Background

PRP is one of the inflammatory keratinization disorders, which is characterized by scaly hyperkeratotic follicular inflammatory papules on extensor surface of the extremities and trunk. Those eruptions often spread, and then present sharply circumscribed orange psoriatic plaques with fine scales. PRP is classified into six subgroups, types I to VI, based on clinical criteria (age of onset, distribution of lesions, disease course and presence/absence of HIV infection). Recently, gain-of-function mutations in *CARD14*, which encodes caspase recruitment domain family member 14 (*CARD14*), were identified in some autosomal dominant familial cases of PRP.

*CARD14* is an activator of nuclear factor kappa-light-chain-enhancer in activated B cells (NFκB) and contributes to inflammatory responses within the epidermis (Fig. 1). Subsequent reports have also implicated *CARD14* variants in various auto-inflammatory skin disorders, although the pathogenic relevance in each disease has not been well determined. To further determine how often PRP patients have pathogenic mutations in *CARD14* and to elucidate which clinical subtype of PRP is caused by *CARD14* mutations.

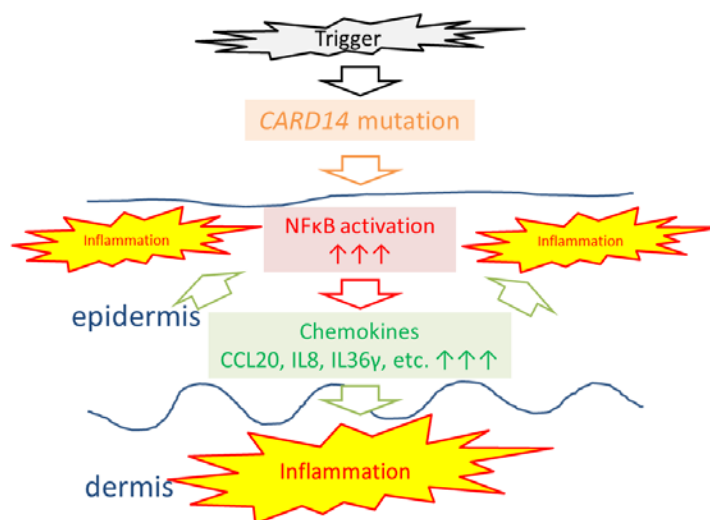


Figure 1.

## Research Results

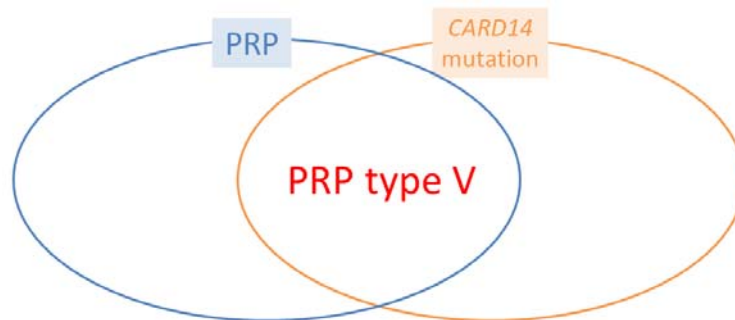
We sequenced the entire coding regions of *CARD14* in genomic DNA from 22 patients with five clinical subtypes of PRP. The detailed clinical features were analyzed in all the patients. Among three PRP type V patients examined, all were found to have *CARD14* mutations: two *de novo* novel mutations, and another previously reported mutation. All were close to the reported pathogenic domains. *In silico* analysis of all three mutations suggested that they are functionally relevant to pathogenesis. All three patients displayed unique patchy macular

brown hyperpigmentation additionally to other typical features of PRP. Patients with PRP type I and type IV, one patient each, had the rare variants in *CARD14*.

### Research Summary and Future Perspective

PRP type V is a distinct variant of PRP that is caused by *CARD14* mutations. In addition, a rare variant of *CARD14* might also be implicated in the pathophysiology of other forms of PRP. Our data suggest that anti-inflammatory therapy targeting *CARD14* may be a promising therapeutic strategy for autoimmune diseases such as PRP type V.

Figure 2.



### Publication

Takuya Takeichi, Kazumitsu Sugiura, Toshifumi Nomura, Taiko Sakamoto, Yasushi Ogawa, Naoki Oiso, Yuko Futei, Aki Fujisaki, Akiko Koizumi, Yumi Aoyama, Kimiko Nakajima, Yutaka Hatano, Kei Hayashi, Akemi Ishida-Yamamoto, Sakuhei Fujiwara, Shigetoshi Sano, Keiji Iwatsuki, Akira Kawada, Yasushi Suga, Hiroshi Shimizu, John A. McGrath, Masashi Akiyama. Pityriasis rubra pilaris type V as an auto inflammatory disease by *CARD14* mutations. *JAMA Dermatology*, Published online before print October 20, 2016.

### Japanese ver.

[http://www.med.nagoya-u.ac.jp/medical/dbps\\_data/material/nu\\_medical/res/topix/2016/prp\\_20161020jp.pdf](http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2016/prp_20161020jp.pdf)