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Research Letter

Autosomal dominant familial generalized pustular psoriasis caused by a *CARD14* mutation

T. Takeichi[1], A. Kobayashi[2], E. Ogawa[2], Y. Okuno[3,4], S. Kataoka[4], M. Kono[1], K. Sugiura[5], R. Okuyama[2], M. Akiyama[1,*]

[1]Department of Dermatology, [4]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Department of Dermatology, Shinshu University, Graduate School of Medicine, Matsumoto, Japan; [3]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan; [5]Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan

*Correspondence: Masashi Akiyama, Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Telephone: 81-52-744-2314

E-mail: makiyama@med.nagoya-u.ac.jp

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Abbreviations: generalized pustular psoriasis (GPP), psoriasis vulgaris (PV), pityriasis rubra pilaris (PRP), psoriatic arthritis (PsA), palmoplantar pustular psoriasis (PPP)

KEY WORDS: generalized pustular psoriasis, psoriasis vulgaris, pityriasis rubra pilaris,

CARD14

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Supplementary files

In 2012, gain-of-function mutations in *CARD14*, which encodes caspase recruitment domain family member 14, were identified as the cause of familial psoriasis vulgaris (PV) and familial pityriasis rubra pilaris (PRP).[1,2] We and another group reported that *CARD14* variants are associated with generalized pustular psoriasis (GPP) and palmoplantar pustular psoriasis (PPP).[3-5] The other reports mentioned that *CARD14* mutations in individuals with GPP and erythrodermic PRP.[4,6] Very recently, we described PRP type V as an autoinflammatory disease caused by *CARD14* mutations.[7]

To date, two individuals with GPP caused by heterozygous *CARD14* mutations have been reported.[1,4] One patient was a member of a familial psoriasis pedigree, but no other member was affected with GPP. The other patient was a sporadic case caused by a *de novo CARD14* mutation. Thus far, there have been no reports of familial GPP caused by a *CARD14* mutation. Here, we describe an autosomal dominant pedigree of GPP (among three generations) associated with *CARD14* mutations. Our findings expand the phenotypic spectrum in CARD14-related autoinflammatory keratinization disorders.

The proband was a 30-year-old female (individual III-2, fig. 1d) with a history of GPP from 6 months of age. She showed diffuse, scaly erythematous lesions with small pustules on the trunk and the extremities (Fig. 1a). Light microscopy of the

affected skin showed acanthosis, marked hyperkeratosis and parakeratosis in the epidermis, and neutrophilic pustules in the upper epidermis. She had been treated with systemic etretinates and cyclosporine A. Then, she had peripheral T-cell lymphoma, not otherwise specified, at the age of 28 years and received 6 cycles of CHOEP (cyclophosphamide, hydroxydaunorubicin, vincristine, etoposide and prednisolone) therapy, followed by an allogeneic bone marrow stem cell transplantation from an unrelated donor (full HLA-matching). Since the transplantation, she has been administered with oral tacrolimus for GVHD, and she has had no skin eruptions. Additional clinical information of the proband's son (IV-1) and father (II-2) are shown in Supplementary files.

Following ethical approval, informed written consent was obtained in compliance with the *Declaration of Helsinki* guidelines. Genomic DNA from patient III-2 was used for whole-exome sequencing analysis, using a methodology described elsewhere.[8] We did not identify potentially pathogenic mutations in *IL36RN* [mutated in deficiency of interleukin 36 receptor antagonist (DITRA)]. However, of interest, a previously reported heterozygous splice-site mutation in *CARD14*, c.349+1G>A, was detected and was then confirmed by Sanger sequencing (data not shown). Her

heterozygous *CARD14* mutation, c.349+1G>A, was also present not only in individuals with GPP [II-2, III-2 (before transplantation) and IV-1], but also in two unaffected family members (II-1 and III-1), suggesting incomplete penetrance. c.349+1G>A does not appear in the Human Genetic Variation Database, which includes 1,208 exome datasets from normal Japanese controls (http://www.genome.med.kyoto-u.ac.jp/SnpDB/index.html).

c.349+1G>A has not been reported previously in PV nor in GPP, but it has been in a family with PRP, although genomic DNA only from two affected family members has been analyzed (possibly incomplete penetrance).[2] Fuchs-Telem *et al.* reported that c.349+1G>A altered the splicing of exon 3 and led to the addition of 66 bp from intron 3 and splicing to exon 4 at a cryptic splice donor site.[2] Additionally, we previously reported a missense mutation of the adjacent base, c.349G>A (p.Gly117Ser), in a PRP patient with incomplete penetrance.[7] c.349G>A has been reported previously in patients with PV, psoriatic arthritis (PsA) and GPP.[1,9] It was also reported that c.349G>A caused the same aberrant splicing as c.349+1G>A does.[1] Taken together, it is possible that other genetic modifications, such as of HLA type, and environmental factors might affect their variable clinical phenotypes. To date, CARD14-mediated psoriasis has been called CAMPS. Here, we propose the new concept of CARD14-related

autoinflammatory keratinization disorders (CAIKD) to expand the phenotypic spectrum of CAMPS (Table 1).

For individual II-2, anti-TNFα antibodies (infliximab), was effective in controlling his eruptions. Coto-Segura *et al.* reported *CARD14* variants affected the anti-TNFα response among patients with psoriasis.[10] Notably, the patient III-2 has been disease-free with systemic tacrolimus treatment since the transplantation. It is difficult to evaluate the efficacy of tacrolimus from only the present case. The further accumulation of GPP cases with mutation data is needed to establish the most effective treatments for CAIKD.

In summary, we reported the first autosomal dominant familial GPP pedigree. In this family, the GPP was associated with *CARD14* mutations. The present family expands the phenotypic spectrum in CAIKD. The present findings, in combination with our previous reports and the literature, suggest that *CARD14* mutants/variants might cause PRP, PV, PsA, PPP and “GPP with PV”, but not “GPP without PV”, with variable penetration rates.

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Figure legends

Figure 1. Clinical features in the present autosomal dominant familial GPP pedigree

(a) The proband (III-2; at age 19 months) shows pustular erythema on the back. (b) The proband's son (IV-1; at age 2 years) shows pustules on background erythema on the chest. (c) The proband's father (II-2; at age 56 years) has pustular erythema on the thighs. (d) The present pedigree with *CARD14* genotypes. G/A means heterozygous carriers of c.349+1G>A. (e) The skin biopsy specimen from the proband's father (II-2) shows acanthosis and hyperkeratosis in the epidermis. Neutrophilic pustules are observed in the upper epidermis. Scale bar = 100 μm.