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Early-onset generalized pustular psoriasis is representative of autoinflammatory keratinization diseases

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To the Editor:

I read with great interest the article titled "Clinical and genetic differences between pustular psoriasis subtypes" by Twelves et al.[1] The authors studied a large number of pustular psoriasis patients, including those with generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH), clinically and genetically. They revealed significant clinical and genetic differences between PPP and GPP.[1]

IL36RN mutant alleles are associated with a phenotypic spectrum of pustular psoriasis that includes ACH and PPP, as well as GPP.[2] Twelves et al.[1] showed that the proportion of patients carrying *IL36RN* mutations is higher in GPP (23.7 %) and ACH (18.2 %) than in PPP (5.2 %). Concerning the concurrence of psoriasis vulgaris (PV) in pustular psoriasis patients, Twelves et al.[1] mentioned that no consistent effect of *IL36RN* mutations was seen on PV concurrence in their study. On this point, we previously reported contrary data that the majority of Japanese GPP patients without PV concurrence have *IL36RN* mutations.[3] In addition, Hussain et al.[4] examined 233 GPP patients and defined a clinical triad (early onset, systemic inflammation, and absence of concurrent PV) to prioritize patients with GPP for *IL36RN* mutation screening. Li et al.[5] reported that Han GPP patients without PV concurrence showed a much higher *IL36RN* mutation frequency than did Han GPP patients with PV concurrence. Thus, the absence of PV concurrence is apparently associated with autoinflammatory pathogenesis due to deficiency of the IL-36 receptor antagonist (IL36Ra) in GPP.

As for the age of onset in pustular psoriasis cases, Twelves et al.[1] showed that *IL36RN* mutations have dose-dependent effects on the age of onset in GPP. I agree with Twelves et al.[1] regarding the association between *IL36RN* mutations and the early age of GPP onset. As mentioned above, Hussain et al.[4] previously revealed that early-onset GPP patients frequently have *IL36RN*

mutations. In addition, Mössner et al.[6] reported a significant correlation between *IL36RN* mutations and early onset in GPP patients.

I summarized the reported data which suggest positive correlations between *IL36RN* mutations and early-onset GPP or GPP without PV concurrence (Table I). Taking these data into consideration, I consider that early-onset GPP without PV concurrence often has an autoinflammatory pathogenesis due to *IL36RN* mutations.

Recently, the umbrella term "autoinflammatory keratinization diseases" (AIKDs) has been proposed.[7] AIKDs encompass inflammatory keratinization disorders with autoinflammatory pathogenesis. The primary and main inflammation sites of AIKDs are the epidermis and the upper dermis, where hyperkeratosis is induced by the inflammation. The hyperactivation of innate immunity (autoinflammation) due to certain genetic factors including deficiency of IL36Ra plays an important role in the pathogenesis of AIKD.[7] From its autoinflammatory pathogenic mechanisms, pustular psoriasis due to *IL36RN* mutations is now regarded as an AIKD.[7]

In this context, early-onset GPP patients without PV concurrence who often have an autoinflammatory pathogenesis due to *IL36RN* mutations might be representative of AIKDs. A better understanding of the pathogenesis of early-onset GPP as an AIKD may provide an important clue for the innovation of novel targeted therapies.

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116 **TABLE I.** Data supportive of positive correlations between *IL36RN* mutations and early-onset GPP or
117 GPP without PV concurrence

Data supportive of correlations between *IL36RN* mutations and early-onset GPP	Reference No.
● *IL36RN* mutation-positive patients show an earlier age of onset. (*IL36RN* mutation-positive GPP patients n=49, mutation-negative patients n=166, P=5.9 X 10^{-7})	4
● The mean age of onset in *IL36RN* mutation heterozygotes exceeds that in patients with biallelic mutations. (GPP patients with heterozygous *IL36RN* mutations n=18, GPP patients with biallelic *IL36RN* mutations n=49, P=6.0 X 10^{-4})	4
● A strong association between biallelic *IL36RN* mutations and early age of onset is observed. (GPP patients with biallelic *IL36RN* mutations n=15, mutation-negative GPP patients n=41, P=7.4 X 10^{-4})	6
● Patients with one or two *IL36RN* mutations have a significantly younger age of onset than that of *IL36RN* mutation-negative patients. (GPP patients with one or two *IL36RN* mutations n=20, mutation-negative GPP patients n=41, P=6.9 X 10^{-3})	6
● *IL36RN* mutations are significantly associated with early age of onset. (*IL36RN* mutation-positive GPP patients n=45, mutation-negative patients n=145, P=0.003)	1
Data supportive of correlations between *IL36RN* mutations and GPP without PV concurrence	
● Patients without PV concurrence show a higher *IL36RN* mutation frequency than that of patients with PV concurrence. (GPP patients without PV concurrence n=11 (9 *IL36RN* mutation-positive patients and 2 mutation-negative patients), GPP patients with PV concurrence n=20 (3 *IL36RN* mutation-positive patients and 17 mutation-negative patients), P<0.01)	3
● Significantly lower concurrence of PV in *IL36RN* mutation-positive patients than that in *IL36RN* mutation-negative patients is observed. (*IL36RN* mutation-positive GPP patients n=49, mutation-negative patients n=166, P=5.0 X 10^{-4})	4
● Patients without PV concurrence exhibit a higher *IL36RN* mutation frequency than that of patients with PV concurrence. (GPP patients without PV concurrence n=24 (19 *IL36RN* mutation-positive patients and 5 mutation-negative patients), GPP patients with PV concurrence n=19 (7 *IL36RN* mutation-positive patients and 12 mutation-negative patients), P<0.05)	5

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