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Mutation analysis of the IL36RN gene in Chinese patients with generalized pustular psoriasis with/without psoriasis vulgaris

Xiuyan Li [a,b,e], Mingfei Chen [a,b], Xi'an Fu [a,b], Qilin Zhang [f], Zhenzhen Wang [a,b], Gongqi Yu [a,b], Yongxiang Yu [a,b], Peipei Qin [a,b,e], Weizhi Wu [c,d], Futang Pan [c,d], Hong Liu [a,b,c,d], Furen Zhang [a,b,c,d,*]

[a] Shandong Provincial Institute of Dermatology and Venereology, Shandong Academy of Medical Sciences, Jinan, Shandong, China
[b] Shandong Provincial Key Lab for Dermatovenereology, Jinan, Shandong, China
[c] Shandong Provincial Hospital for Skin Diseases, Shandong University, Jinan, Shandong, China
[d] Shandong Provincial Medical Center for Dermatovenereology, Jinan, Shandong, China
[e] School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, Jinan, Shandong, China
[f] School of Medicine, Shandong University, Jinan, Shandong, China

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ABSTRACT

Background: Generalized pustular psoriasis (GPP) is a rare type of psoriasis with potentially life-threatening implications. Mutations in IL36RN gene have been suggested to be causative or predisposing factors for GPP.
Objective: To evaluate the genetic heterogeneity of GPP, PV and GPP alone, GPP with PV.
Methods: We performed a sanger sequencing identify IL36RN mutations in 62 Chinese Han patients with sporadic GPP, including 17 GPP without psoriasis vulgaris (PV) (GPP alone) cases vs. 45 GPP with preceding, later or accompanied by PV (GPP with PV) cases; 16 patients with pediatric-onset GPP (PGPP) vs. 46 adult-onset GPP (AGPP). We included 96 healthy controls and 174 sporadic patients with PV.
Resuts: We found 2 new variants and 4 known IL36RN variants in 29 GPP patients, 18 individuals carried recessive (homozygous/compound heterozygous) alleles and 11 cases harbored a single heterozygous change. Twelve PV patients and six controls harbored a single heterozygous for three out of the six variants.
Significant differences were observed between GPP and PV groups, GPP alone and GPP with PV groups when compared frequencies of IL36RN variants, but we did not found association between PGPP and AGPP groups.
Conclusion: Our study provided more evidence that GPP and PV are distinct subtypes of psoriasis caused by different pathogenesis, and GPP alone could be regarded as an especial entities of GPP which is different from GPP with PV on the etiology.

1. Introduction

Generalized pustular psoriasis (GPP) is a rare type of psoriasis characterized by sudden and repeated episodes of generalized rash and disseminated pustules, often accompanied by high-grade fever. GPP could be divided into different subtypes: GPP without psoriasis vulgaris (PV) (GPP alone) vs. GPP with PV [1], and pediatric-onset GPP (PGPP) vs. adult-onset GPP (AGPP) [2].

The susceptibility background of the host has been proven to play a critical role in the onset and development of GPP. Marrakchi et al. firstly reported a homozygous mutation p.Leu27Pro of *IL36RN* gene in familial GPP patients [3]. Since then the widely use of sequencing has led to identify 14 mutations of *IL36RN* as causative or predisposing factors in some sporadic cases of GPP [1,2,4–9].

And also diverse genetic heterogeneity has been reported in different subtypes of GPP: the associations of these mutations were stronger with the GPP alone form than with the GPP with PV form in Japanese population [1]; the percentage of *IL36RN* mutations of PGPP patients was much higher than that of AGPP patients in Chinese population [2].

On the other hand, although GPP is traditionally held to be a variant of psoriasis, it has been demonstrated that loss of IL36RN function did not confer susceptibility to PV in British and Chinese populations [2,7,10], implying that heritable factors might play different roles in GPP and PV patients.

* Corresponding author at: Shandong Provincial Institute of Dermatology and Venereology, 27397 Jingshi Road, Jinan, Shandong Province 250022, China. Tel.: +86 531 87298801; fax: +86 531 87984734.
E-mail addresses: zhangfuren@hotmail.com, zhangfuren1027@163.com (F. Zhang).

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Table 1
Descriptive characterization of patients with GPP, PV and control.

Type	Male/female	Age (years) mean ± SD	Age at onset (years) of GPP mean ± SD	Number
GPP	38/24	36.70 ± 17.54	33.10 ± 19.77	62
GPP alone	9/8	31.98 ± 23.00	23.50 ± 24.46	17
GPP with PV	29/16	38.48 ± 14.91	36.73 ± 16.59	45
PGPP	8/8	16.02 ± 12.39	6.15 ± 4.94	16
AGPP	30/16	43.89 ± 12.69	42.48 ± 13.18	46
PV	88/86	45.99 ± 20.79	29.31 ± 21.83[a]	174
Control	50/46	40.23 ± 8.97		96

GPP: generalized pustular psoriasis; PV: psoriasis vulgaris; GPP alone: GPP without PV; GPP with PV: GPP with preceding or accompanied by PV; PGPP: pediatric-onset generalized pustular psoriasis; AGPP: adult-onset generalized pustular psoriasis.
[a] Age at onset (years) of PV mean ± SD.

Taken together, may GPP with PV be a severe form of PV with pustule outbreak? More evidence remains clarified in different populations.

In order to evaluate the genetic heterogeneity of GPP, PV and GPP alone, GPP with PV, we have performed a sanger sequencing to identify *IL36RN* mutations in Chinese Han sporadic GPP and PV patients.

2. Materials and methods

2.1. Subjects

A total of 62 sporadic and non-consanguineous GPP, 174 with PV and 96 controls from Chinese Han were included in the analysis. All GPP patients showed generalized erythema and disseminated pustules, often accompanied by high-grade fever, neutrophilia, and elevated C-reactive protein. Skin biopsy showed spongiform pustules of Kogoj in the subcorneal portion of the epidermis. GPP cases were classified into two sets of groups: GPP without PV (GPP alone; 17 cases); GPP with preceding, later or accompanied by PV (GPP with PV; 45 cases); patients who developed GPP before the age of 18 years were further designated as pediatric-onset GPP (PGPP; 16 cases) vs. others were recognized as adult-onset GPP (AGPP; 46 cases). Individuals in the PV group had at least two psoriatic scales or a single scale occupying at least 1% of the total body surface outside the scalp, and all had a clinical history of psoriasis at least 10 years. All patients were diagnosed by experienced dermatologists based on typical clinical presentations or histopathological findings. Controls were unaffected individuals with no family history of psoriasis, recruited from the Health Examination Center. The characteristics of the different groups are summarized in Table 1, as well as described in Fig. 1.

This study was approved by the human medical and ethics committee of Shandong Provincial Institute of Dermatology and Venereology. We have received signed forms of informed consent from all the participants in this study.

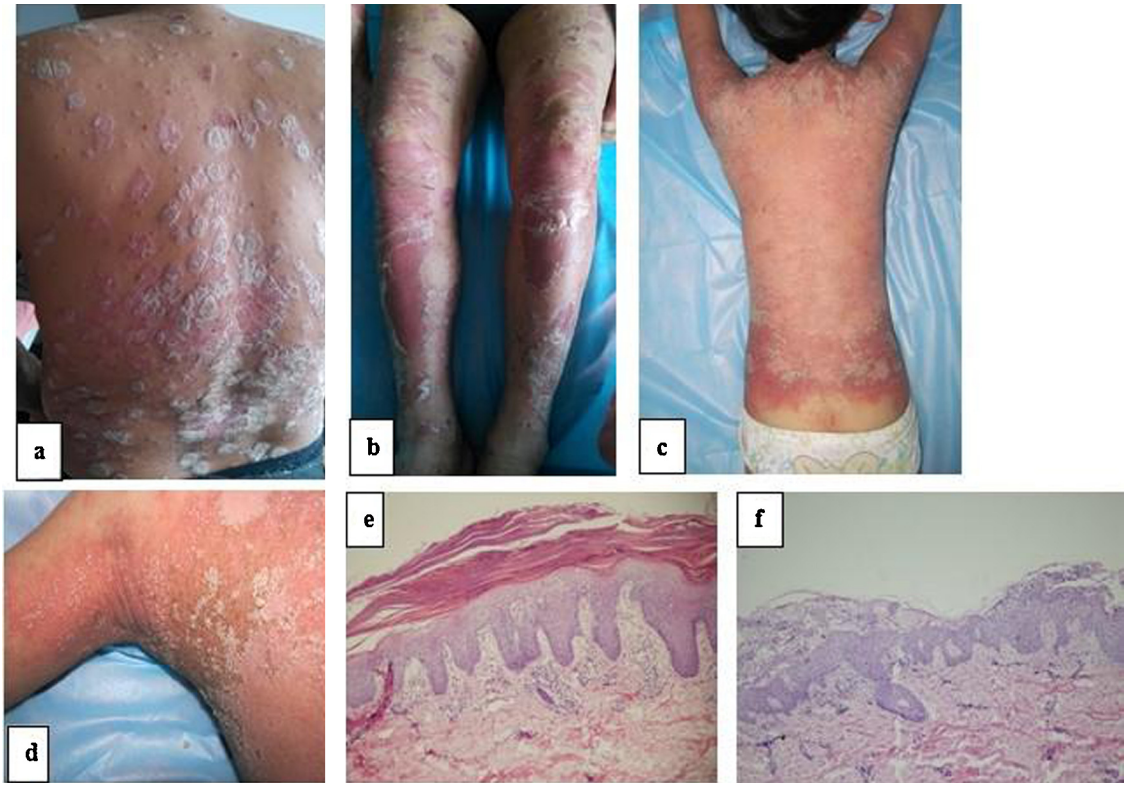

Fig. 1. Representative clinical and pathological features of psoriasis vulgaris and generalized pustular psoriasis. (a, b) Psoriasis vulgaris (PV). Well-demarcated scaly, red plaques are observed on the trunk. Cutaneous inflammation progresses to exfoliative dermatitis over the legs. (c, d) Generalized pustular psoriasis (GPP). Pustules on background erythema are seen on the trunk and arms. (e) Histopathological features of a typical psoriatic plaque in a PV patient. Characteristic features of psoriasis, acanthosis, hyperkeratosis and parakeratosis are seen in the epidermis. (f) Histopathological features of pustular lesions in patient with GPP. The epidermis shows thickening with regular elongation of rete ridges. The characteristic spongiform pustules of Kogoj are clearly observed in the epidermis of pustular lesions.