An update on genetic basis of generalized pustular psoriasis (Review)

JIAHONG ZHOU, QING LUO, YANG CHENG, XIA WEN and JINBO LIU

Department of Laboratory Medicine, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000, P.R. China

Received October 18, 2020; Accepted March 11, 2021

DOI: 10.3892/ijmm.2021.4951

Correspondence to: Professor Jinbo Liu, Department of Laboratory Medicine, Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Luzhou, Sichuan 646000, P.R. China
E-mail: liulab2019@163.com

Key words: generalized pustular psoriasis, mutation, IL36RN gene, CARD14 gene, APIS3 gene, MPO gene, pathoimmunology, biologics treatment, heterogeneity

Abstract. Generalized pustular psoriasis (GPP) is a rare and severe auto-inflammatory skin disease that is characterized by recurrent, acute onset, and generalized pustular eruptions on erythematos, inflamed skin. GPP is traditionally classified as a variant of psoriasis vulgaris, even though recent clinical, histological and genetic evidence suggests that it is a heterogeneous disease and requires a separate diagnosis. In recent years, variants of IL36RN, CARD14, APIS3 and MPO genes have been identified as causative or contributing to genetic defects in a proportion of patients affected by GPP. These disease-related genes are involved in common inflammatory pathways, in particular in the IL-1/IL-36-chemokines-neutrophil pathogenic axis. At present, no standard therapeutic guidelines have been established for GPP management, and there is a profound need for novel efficacious treatments of GPP. Among them, biological agents antagonizing the IL-36 pathway are promising therapeutics. The aim of the present review is to provide the most recent updates on the genetics, genotype-phenotype correlation and pathological basis of GPP, as well as on biologic treatments available for GPP and relative clinical courses.

1. Introduction

Generalized pustular psoriasis (GPP) is a rare and severe auto-inflammatory skin disease with life-threatening potential that is characterized by recurrent and sudden episodic generalized erythematos eruptions with neutrophil-filled pustules (1,2). GPP is accompanied by high fever, leukocytosis and elevated serum levels of C-reactive protein in the acute phase, and can be triggered by infections, pregnancy or drugs (1,2). GPP is an extremely rare form of psoriasis with an estimated prevalence of 7.46 patients per million in Japan (3) and 1.76 patients per million in France (4), and represents about 1% of all clinical types of psoriasis (5-8). Histologically, GPP is characterized by Kogoj's spongiform pustule and Munro's microabscesses with a large number of infiltrating neutrophils (9,10). GPP is clinically heterogeneous in presentation and progression, and currently lacks consistent classification. Concerning clinical presentation, GPP is considered one of the distinct subtypes of pustular psoriasis (PP), which can present as a recurrent systemic illness (GPP) or chronic localized form affecting palms and/or soles (palmoplantar pustulosis, PPP), or digits/nail beds (acrodermatitis continua of Hallopeau, ACH) (1,11,12). Since GPP often presents in individuals with an existing history of psoriasis vulgaris (PV), it can be divided into two subtypes, namely GPP alone and GPP with PV. Patients affected by GPP alone generally carry genetic variations of IL36RN and show more severe clinical symptoms, early acute onset of the disease, repeated and persistent attacks, and systemic inflammation (13,14). According to age of onset, GPP can be classified into pediatric-onset GPP (≤18 years) and adult-onset GPP, with pediatric-onset GPP manifesting mostly as GPP alone and occurring with recurrent and sudden systemic inflammation (15-17). GPP, especially the pediatric-onset GPP form, is considered to be an independent subtype of psoriasis which differs from PV and requires a distinct diagnosis.

Although the first GPP case was reported in 1910, its etiology and detailed pathogenesis have been only recently described in the literature. In 2011, the identification of loss-of-function mutations in IL36RN gene emphasized the key role of this pathway in the pathogenesis of GPP (18). Since then, an increasing number of genetic variants in CARD14, APIS3, and MPO pathogenic genes have been found to be associated with GPP in affected individuals (19-21). Subsequent to the identification of disease-causing genes, the pathogenesis
of GPP has progressively been characterized and new specific biological agents have been developed.

In the present review, the aim was to assess current knowledge on the genetic basis and molecular details of the cutaneous pathomechanisms and specific treatments available on GPP and relative clinical courses.

2. Mutation update on disease-causing gene associated with GPP

In recent years, a number of allelic variations and mutations in IL36RN, CARD14, API3S genes, as well as in the latest identified pathogenic MPO gene have been found to be associated with GPP (18-21). Among those genes, IL36RN mutations are the most frequent genetic abnormality (22,23), CARD14 mutations are primarily present in GPP with PV and rarely in GPP alone(24,25). The pathogenic variants of API3S were mainly found in individuals of European origin and rarely in East Asians (20,26).

Disease-causing gene IL36RN
Pathogenic mechanism underlying IL36RN mutations. Mutations in IL36RN gene are likely to be the main molecular genetic basis defect in patients affected by GPP (22). Interleukin-36 (IL-36) refers to three related IL-1 family cytokines, IL-36α, IL-36β, and IL-36γ, which can activate the downstream pro-inflammatory nuclear factor-κB and mitogen-activated protein kinase (MAPK) pathways by binding to IL-36 receptor (IL-36R). Subsequently, IL-36s induce the release of inflammatory mediators and chemotaxis that promote activation of neutrophils, macrophages, dendritic cells, and T cells, ultimately causing the amplification of inflammatory responses (27). IL-36 receptor antagonist (IL-36Ra) encoded by IL36RN gene is specifically expressed by epidermal keratinocytes (28) and can compete with IL-36 via binding to IL-36R, thereby blocking the inflammatory responses caused by IL-36 itself (29). The loss of function mutations in IL36RN gene results in the inability of IL-36Ra to antagonize and limit the pro-inflammatory effects of IL-36 (18,30), thereby leading to increased expression of pro-inflammatory cytokine regulated by transcription factor NF-κB and MAPK, such as IL-8, CXCL1-3, IL-1, and even IL-36 itself, thus forming a vicious cycle of enhancing inflammation. IL-8 and CXCL1-3 are strong neutrophil chemokines and the upregulation of their expression contributes to the neutrophils infiltrating in skin pustules and systemic inflammation of GPP patients (31).

Identification of the IL36RN gene mutations in GPP patients. In 2011, Marrakchi et al (18) first reported that 9 familial Tunisian GPP patients carried the c.80T>C (p.Leu27Pro) homozygous missense mutation in IL36RN, which determines increased keratinocyte expression of the inflammatory cytokines in GPP patients, such as IL-8, IL-36α, IL-36β, and IL-36γ. Therefore, IL36RN was identified as a causative gene for GPP patients and the disease caused by IL-36Ra decrease was defined as deficiency of interleukin-1-receptor antagonist (DIRA), an autoinflammatory disease related to activation of the IL-1 pathway, even if they suffered from similar skin manifestations (18,32,33,34). Then, Onoufriadis et al (30) revealed the c.338C>T (p.Ser113Leu) homozygous missense substitution and the c.338C>T (p.Ser113Leu) and c.142C>T (p.Arg48Trp) compound heterozygote missense mutations in IL36RN gene in sporadic GPP cases in the UK. Subsequently, a set of functional relevant variants in IL36RN gene, such as c.28C>T (p.Arg10X), c.104A>G (p.Lys35Arg), c.140A>G (p.Asn47Ser), c.227C>T (p.Pro76Leu), c.304C>T (p.Arg102Trp), c.305G>A (p.Arg102Gln), c.368C>G (p.Thr123Arg), c.368C>T (p.Thr123Met), and c.115+6T>C (p.Arg10AsfsX1), were identified in GPP patients of Eastern Asia (15,35-37). According to sequencing and functional analysis of GPP patients from different populations, a total of 25 possible pathogenic variants in the IL36RN gene have been reported thus far (Fig. 1A and Table I). The majority of these genetic variants are missense substitutions, or to a lesser extent, nonsense mutations. The latter include c.28C>T (p.Arg10X), c.41C>A (p.Ser14X), c.280G>T (p.Glu94X) and c.338C>A (p.Ser113X) mutations that generate termination codons after the base substitutions. In addition, the c.115+6T>C mutation in a splicing site of IL36RN causes the skipping of exon3 at mRNA level, leading to a frameshift and premature protein termination (p.Arg10AsfsX1) (37). Furthermore, small fragment deletions (c.420_426del and c.295-300del) have been also identified in GPP patients. The c.420_426del mutation in exon 5 results in a frameshift starting from the amino acid 140, as well as in premature stop codon formation at position 170 (38). On the other hand, the c.295-300del variant leads to thr99 and phe100 amino acid deletion (23). Although the c.338C>T substitution is the most frequent variant in Europeans (39) c.115+6T>C is the most common in Asian populations (37,40-42). In vitro functional assays have shown that IL36RN gene pathogenic mutations lead to a decrease in the expression or activity of IL36Ra and increase of IL-36-dependent pro-inflammatory factors activated by NF-κB pathway (i.e., IL-1β, IL-8, IL-36). For instance, the c.80T>C (p.Leu27Pro), c.28C>T (p.Arg10X), c.280G>T (p.Glu94X), c.368C>G (p.Thr123Arg), c.368C>T (p.Thr123Met) and c.227C>T (p.Pro76Leu) homozygous missense mutations result in functional impairment of IL-36Ra protein expression and capacity to suppress downstream inflammatory responses (38). However, the function of some variants remains to be elucidated. Interestingly, homozygous or heterozygous variants in IL36RN gene, such as c.115+6T>C, have also been identified in healthy cohorts (15). Findings of those studies indicate that the onset of GPP depends on a combination of multiple genetic factors, rather than a single inherited gene.

Genotype-phenotype correlation. Since some GPP cases are accompanied by PV, Sugiura et al (13) first screened the IL36RN gene in two subgroups of GPP patients in the Japanese population (GPP alone and GPP with PV, respectively), showing that all the GPP patients without PV (n=11) harbored homozygous or compound heterozygous mutations in IL36RN gene (13,48), whereas only 2 out of 20 cases of GPP with PV carried compound heterozygous mutations. Since the frequency of IL36RN mutations in patients of
| Nucleotide variations | Amino acid variations | Variant type | Status of the mutations | Origin | Protein expression | Inflammation inhibition |
|-----------------------|----------------------|--------------|-------------------------|--------|-------------------|-------------------------|
| c.28C>T               | p.Arg10X             | Nonsense     | Hom/CHet                | Japanese/Palestinian | None | Impaired           | (13,35-38,43,44)       |
| c.41C>A               | p.Ser14X             | Nonsense     | Hom                     | Algerian | None | Impaired           | (38)                   |
| c.62T>C               | p.Leu21Pro           | Missense     | Hom                     | Pakistani | Not reported | Not reported | (45)                   |
| c.80T>C               | p.Leu27Pro           | Missense     | Hom                     | Tunisian | None | Impaired           | (18,38,46)             |
| c.95A>G               | p.His32Arg           | Missense     | Hom                     | Iraqi | Reduced | Impaired | (23,38,47)             |
| c.104A>G              | p.Lys35Arg           | Missense     | Het/CHet                | British | Unchanged | Unchanged | (22,38,39)             |
| c.125T>A              | p.Ile42Asn           | Missense     | Hom                     | Japanese | Not reported | Not reported | (48)                   |
| c.130G>A              | p.Val44Met           | Missense     | CHet                    | Chinese/ German | Not reported | Not reported | (22,23,42)             |
| c.140A>G              | p.Asn47Ser           | Missense     | Hom/CHet/ Het           | Chinese | Not reported | Not reported | (15,16,42,49)         |
| c.142C>T              | p.Arg48Trp           | Missense     | Het/CHet                | British/ German | Reduced | Reduced | (22,23,30,38,47)      |
| c.169G>A              | p.Val57Ile           | Missense     | Het                     | Chinese | Not reported | Not reported | (16)                   |
| c.227C>T              | p.Pro76Leu           | Missense     | Hom/CHet/ Het           | Chinese/ Turkish/ German/ Bosnian/ Syrian/ Malay | Not reported | Not reported | (15,16,22,23,38,42,47,49) |
| c.245C>T              | p.Pro82Leu           | Missense     | Het                     | Chinese | Not reported | Not reported | (16)                   |
| c.280G>T              | p.Glu94X             | Nonsense     | Hom/CHet/ Het           | British/ Turkish/ East Asian | Not reported | Not reported | (23,39,47)             |
| c.304C>T              | p.Arg102Trp          | Missense     | Hom/CHet/ Het           | British/ Turkish/ East Asian | Not reported | Not reported | (22,38,39,42)         |
| c.305G>A              | p.Arg102Gln          | Missense     | Het                     | Chinese | Not reported | Not reported | (15)                   |
| c.308G>A              | p.Arg103Gln          | Missense     | Het                     | Chinese | Not reported | Not reported | (23)                   |
| c.334G>A              | p.Glu112Lys          | Missense     | CHet                    | British/ German/ Iraqi/ Swiss/ Russian | Not reported | Not reported | (49)                   |
| c.338C>T              | p.Ser113Leu          | Missense     | Hom/CHet/ Het           | Japanese/ Chinese/ Malay/ Korean/ German | Not reported | Not reported | (17,22,23,30,38,39,47,50) |
| c.338C>A              | p.Ser113X            | Nonsense     | CHet                    | Russian | Not reported | Not reported | (23)                   |
| c.368C>G              | p.Thr123Arg          | Missense     | CHet                    | Japanese | None | Impaired | (37,38)               |
| c.368C>T              | p.Thr123Met          | Missense     | CHet                    | Japanese/ Chinese | None | Impaired | (16,36,38)             |
| c.115+6T>C            | p.Arg10ArgfsX1       | Frameshift   | Hom/CHet/ Het           | Japanese/ Chinese/ Malay/ Korean/ German | Not reported | Not reported | (13,15-17,22,37,39,42,49,51-53) |
| c.295-300del          | p.Thr99_Phe100del    | Small fragment deletion | CHet | Japanese/ German | Not reported | Not reported | (23)                   |
| c.420_426del          | p.Gly141MetfsX29     | Frameshift   | Hom                     | Spanish/ Algerian | None | Impaired | (17,38)               |

Hom, homozygous; Het, heterozygous; CHet, compound heterozygous.
GPP alone was much higher than that observed in patients with both GPP and PV forms. Sugiuira et al (13) suggested that GPP alone represents a distinct subtype of GPP and is etiologically distinguishable from GPP occurring with PV. In 2014, the genetic heterogeneity in different subtypes of GPP also was validated in a study analyzing IL36RN mutations in GPP Chinese patients (16). Consistently, the meta-analysis of 233 GPP patients by Hussain et al in 2015 (17) revealed that carriage of IL36RN mutations manifested early onset of the disease (17±2.4 years vs. 33±1.5 years; P=5.9x10⁻³), higher risk of systemic inflammation (83 vs. 56%; P=1.5x10⁻³), and lower prevalence of PV (36.1 vs. 68.7%, P=5x10⁻⁴). Of note, findings of that study also demonstrated that the number of mutant alleles of IL36RN gene also correlated with a younger age of onset. In 2017, further genotype-phenotype correlation analysis of 66 Chinese children with GPP alone also validated that IL36RN-positive cases manifested a more severe clinical phenotype, characterized by early onset, severe inflammation in skin lesions, and high recurrence rate following treatment with low-dose acitretin (42). In 2019, a survey including a cohort of 251 cases of GPP patients from multiple countries also showed IL36RN gene mutations associated with the age of onset, prevalence of PV, and recurrence rate of GPP (22). Taken together, the aforementioned studies demonstrated that IL36RN gene mutations are, not only related to the pathogenesis of GPP, but also to the clinical phenotype associated to GPP (Table II).

**Table II. Studies of correlation between IL36RN mutations and clinical phenotype.**

| Studies, year | Origin | No. of patients enrolled | Low prevalence of PV | Early age of onset | Severe inflammation | High recurrence rate | (Refs.) |
|--------------|--------|--------------------------|----------------------|-------------------|-------------------|---------------------|---------|
| Sugiuira et al, 2013 | Japanese | 31 | Y | N/A | N/A | N/A | (13) |
| Li et al, 2014 | Chinese | 62 | Y | N/A | N/A | N/A | (16) |
| Hussain et al, 2015 | European, Asian, African | 233 | Y | Y | Y | N/A | (17) |
| Wang et al, 2017 | Chinese | 66 | N/A | Y | Y | Y | (42) |
| Twelves et al, 2019 | European, East Asian, Malay | 251 | Y | Y | N/A | Y | (22) |

Y, yes; N/A, not applicable.

**Disease-causing gene CARD14.** CARD14 gene, also known as CARMA2 gene, encodes caspase recruitment domain family member 14 (CARD14) which mediates the activation of TRAF2-dependent NF-xB signaling in keratinocytes (54,55). CARD14 expression is mostly restricted to the basal layer of epidermis in healthy skin, whereas it is upregulated in the granular layers in GPP-affected skin (19).

In 2012, Jordan et al (19) identified the c.349G>A (p.Gly117Ser) and c.349+5G>A heterozygosity in CARD14 gene in European ancestry with psoriasis, and the c.413A>C (p.Glu138Ala) variant in a sporadic pediatric case with GPP. The gain-of-function mutations of c.413A>C and c.349+5G>A caused enhanced NF-xB activation in keratinocytes and upregulation of a subset of psoriasis-associated genes, in particular chemokine (C-C motif) ligand 20 (CCL20), and IL8 genes. Then, the group of Jordan continued to expand the number of cohorts (56), further screening more than 6,000 psoriasis patients and 4,000 controls in multiple regions. Those studies identified 15 novel rare missense mutations, among which the c.425A>G (p.Glu142Gly) and c.424G>A (p.Glu142Lys) mutations resulting in, respectively, 4- and 5-fold activation of NF-xB, as compared with wild-type allele. On the other hand, c.511C>A (p.His171Asn) and c.536G>A (p.Arg179His) variants significantly activated the NF-xB pathway after the stimulation of tumor necrosis factor-α (TNF-α). The expression of 13 inflammatory genes (e.g., CCL20, IL8, IL6, colony stimulating factor 2, CSF2) was also described to be upregulated in keratinocytes of patients with CARD14 gene variants (56).

The aforementioned studies have shown that the gain-of-function mutations of CARD14 gene are associated with psoriasis, but the relationship between CARD14 gene and GPP remains to be adequately elucidated. In 2014, Sugiuira et al (24) found that 4 out of 19 cases of GPP with PV carried the c.526G>C (p.Arg179His) heterozygous missense mutations in CARD14 gene in a Japanese cohort, and the frequency of allelic mutations was significantly higher than that of controls (3/100) and of patients with PV (4/100). Thus, Sugiuira et al suggested that c.526G>C mutation is an important risk factor for GPP with PV, and is distinct from the PV form. However, no pathogenic variants in the CARD14 gene were identified in 11 patients affected by GPP without PV, which supports that GPP alone is a heterogeneous disease and genetically different from GPP with PV. Subsequently, Qin et al (57) identified two novel heterozygous mutations, the c.355A>G (p.Met119Val) and c.497G>A (p.Arg166His), in 62 Chinese patients suffering from GPP with PV, with the frequency of allelic mutations being significantly higher than that of controls (0/365), but similar to that detected in patients with PV (2/174). In 2015, a significant association between pathogenic c.526G>C mutation and GPP in Asian populations was revealed by the analysis of 105 individuals affected by GPP (58). Subsequently, the group of Mössner (23) and Twelves (22) identified CARD14 variants...
in patients, even though they were rarely found in patients with GPP. Mössner et al (23) also identified 3 heterozygous missense mutations in CARD14 gene, the c.206G>A (p.Arg69Gln), c.349G>A, and c.536G>A, in 51 GPP cases, and Twelves et al (22) reported that only 3 out of 251 GPP patients harbored the c.526G>C heterozygous mutation. Taken together, 10 possible pathogenic variants of CARD14 gene have been identified (Fig. 1B, Table III), even though they are not common in GPP patients. Among them, the c.526G>C missense mutation, found in the Asian population, is the most common. Mutations in CARD14 gene are mainly presented in GPP patients concomitantly affected by PV and rarely showing GPP alone (20,26). CARD14 gene mutations specific for PV and GPP patients have not been characterized yet. Therefore, the correlation between CARD14 gene mutations and the onset of GPP remains to be further elucidated.

Disease-causing gene API33. API33 gene, encoding the core subunit σ1C of adaptor protein complex 1 (AP-1), is responsible for the stabilization of AP-1 heterotetramers involved in vesicular trafficking between the trans-Golgi network and endosomes. Findings have shown that loss-of-function mutations of API33 gene are relevant in GPP. In 2014, Setta-Kaffetz et al (20) identified heterozygosity for the c.11T>G (p.Phe4Cys) and c.97C>T (p.Arg33Trp) missense mutations in API33 gene in 15 European patients with various forms of pustular psoriasis (i.e., PPP, ACH, and GPP) and not harboring IL36RN and CARD14 gene mutations (Fig. 1C).

Figure 1. Genomic structure of GPP-related genes and location of the identified variants. Exons and relative non-coding introns of (A) IL36RN, (B) CARD14, (C) API33 and (D) MPO genes were shown by solid black and gray boxes, respectively. Blue, red, purple and green boxes represent, respectively, missense, nonsense and frameshift mutations, as well as small fragment deletions. Asterisks indicate the mutations that have been validated by functional assays. The red triangle represents the affected IL-36R binding site after nucleotide substitution, and daggers indicate that the CARD14 mutations only characterized in PV patients.
Table III. Mutations of CARD14 gene and related characteristics in GPP patients.

| Nucleotide variations | Amino acid variations | Variants type | Status of the mutations | Origin | Effect on NF-κB activation (vs. wild-type) | (Refs.) |
|-----------------------|----------------------|---------------|-------------------------|--------|-----------------------------------------|--------|
| c.349G>A              | p.Gly117Ser          | Missense      | Het                     | European/ German | 3.71  | (19,23,56) |
| c.355A>G              | p.Met119Val          | Missense      | Het                     | Chinese | Not reported | (57) |
| c.413A>C              | p.Glu138Ala          | Missense      | Het                     | Haitian | 8.95  | (19,56) |
| c.497G>A              | p.Arg166His          | Missense      | Het                     | Chinese | Not reported | (57) |
| c.526G>C              | p.Aspl76His          | Missense      | Het                     | Japanese/ Chinese | 2.78  | (22,24,25, 56,58) |
| c.536G>A              | p.Arg179His          | Missense      | Het                     | German  | 1.38  | (23,56) |
|                        |                     |               |                         |         | 1.38  | (23,56) |
| c.424G>A†             | p.Glu142Lys          | Missense      | Het                     | Not reported | 4.03  | (56) |
| c.425A>G†             | p.Glu142Gly          | Missense      | Not reported            | 5       | (56) |
| c.511C>A†             | p.His171Asn          | Missense      | Not reported            | 0.68   | (5.95 with TNF-α stimulation) | (56) |
| c.824G>A†             | p.Arg275His          | Missense      | Not reported            | Not reported | Not reported | (56) |
| c.349+5G>A†           | Alter splice of intron | Frameshift    | Het                     | Taiwanese | Not reported | (19) |

†Only characterized in PV patients; Hom, homozygous; Het, heterozygous.

In parallel, these pathogenic variants were not detected in 70 cases from Africa and Asia. In vitro functional assays demonstrated that the substitution of c.11T>G causes a significant reduction in protein expression, and silencing of AP1S3 in human keratinocytes and HEK293 cells abolishes endosomal translocation of toll-like receptor-3 (TLR3) and TLR3-dependent expression of interferon-β1 (IFNB1) following induction with polynosinic-polycytidylic acid [poly(I:C)], an agonist of TLR3 involved in responses to viral infections. Thus, Setta-Kaffetzzi et al (20) proposed that defects in vesicular trafficking may be an important pathological basis for auto-inflammatory in pustular psoriasis. In 2016, Mahil et al (26) further demonstrated that knockout of AP1S3 gene disrupts autophagy in keratinocytes, thereby resulting in abnormal accumulation of p62, which mediates NF-κB activation and upregulation of IL-1, IL-36α and other cytokines. Subsequently, the c.11T>G and c.97C>T heterozygous mutations in AP1S3 gene were detected in two European patients with GPP, and the novel c.64A>G (p.Thr22Ala) homozygous variant have been found in patients with AGEP. Of note, all three variants have been repeatedly observed in individuals affected by myeloperoxidase deficiency (MPOD) in which MPO deficiency and the onset of GPP has been characterized (21,59). Although previously described in a single case with pustular psoriasis (60,61), MPO deficiency was not recognized as a genetic risk factor of GPP until 2020 (4), when genetic variants in MPO gene were screened in GPP and in conditions phenotypically related to GPP, such as acral pustular psoriasis (APP) and acute generalized exanthematous pustulosis (AGEP). Vergnano et al (21) first identified the c.2031-2A>C homozygous mutation due to A-C transition in the 3’ end of intron 11 in MPO gene in patients with GPP or APP, and resulting in activation of a cryptic 3’ splice site located 109 bp upstream of canonical 3’ splice site, thereby causing a 119-bp fragment insertion and a shift of the reading frame leading to premature protein truncation. In addition, the c.2031-2A>C and c.1705C>T (p. Arg569Trp) compound heterozygous mutations and c.1555_1568del homozygous variant have been found in patients with AGEP. Of note, all three variants have been repeatedly observed in individuals affected by myeloperoxidase deficiency (MPOD) in which MPO gene variants cause impairment of MPO protein function (62-64). Phenome-wide association studies (pheWAS), which provide a way to identify important relationships between genetic variants and a wide array of phenotypes, and in vitro functional analysis demonstrated that mutations in MPO gene cause an increase of neutrophil accumulation and activity, as well as a reduction in the number of apoptotic neutrophils induced by phorbol myristate acetate (PMA), thus suggesting a role of MPO mutations in GPP pathogenesis. Haskamp et al (59) further confirmed the important role of MPO gene defects in the pathogenesis of GPP. In fact, they showed that 15 out of 74 patients with GPP carried 8 variants in MPO gene, including the following: The c.265_275dup11

Disease-causing gene MPO. MPO gene encodes myeloperoxidase, a lysosomal hemoprotein located in the azurophilic granules of neutrophils. The correlation between MPO deficiency and the onset of GPP has been characterized only recently (21,59). Although previously described in a single case with pustular psoriasis (60,61), MPO deficiency was not recognized as a genetic risk factor of GPP until 2020 (4), when genetic variants in MPO gene were screened in GPP and in conditions phenotypically related to GPP, such as acral pustular psoriasis (APP) and acute generalized exanthematous pustulosis (AGEP). Vergnano et al (21) first identified the c.2031-2A>C homozygous mutation due to A-C transition in the 3’ end of intron 11 in MPO gene in patients with GPP or APP, and resulting in activation of a cryptic 3’ splice site located 109 bp upstream of canonical 3’ splice site, thereby causing a 119-bp fragment insertion and a shift of the reading frame leading to premature protein truncation. In addition, the c.2031-2A>C and c.1705C>T (p. Arg569Trp) compound heterozygous mutations and c.1555_1568del homozygous variant have been found in patients with AGEP. Of note, all three variants have been repeatedly observed in individuals affected by myeloperoxidase deficiency (MPOD) in which MPO gene variants cause impairment of MPO protein function (62-64). Phenome-wide association studies (pheWAS), which provide a way to identify important relationships between genetic variants and a wide array of phenotypes, and in vitro functional analysis demonstrated that mutations in MPO gene cause an increase of neutrophil accumulation and activity, as well as a reduction in the number of apoptotic neutrophils induced by phorbol myristate acetate (PMA), thus suggesting a role of MPO mutations in GPP pathogenesis. Haskamp et al (59) further confirmed the important role of MPO gene defects in the pathogenesis of GPP. In fact, they showed that 15 out of 74 patients with GPP carried 8 variants in MPO gene, including the following: The c.265_275dup11
GPP is considered a typical one (66,67). Thus, initial genetic causative factors related to the hyperactivation of innate comprises inflammatory keratinization disorders with genetic keratinization disease (AiKD) has been designated to MPO result in an increased expression of CXCL1-3, IL-1, IL-8, and homozygous variants, the c.1555_1568del (p.Met519Profs*21) heterozygous variants (Fig. 1D). All these variants were validated as loss-of-function mutations, and, among them, 5 missense mutations (c.1768C>T, c.1705C>T, c.1642C>T, c.752T>C (p. Met251Thr), c.995C>T (p.Ala332Val), c.2031-2A>C (p.Phe678 nonsense variants, the c.995C>T (p.Ala332Val) and c.265_275dup11 homozygous mutation determined a lack of MPO expression in neutrophils, the c.2031-2A>C substitution in a splicing site as well as the c.1555_1568del deletion resulted in a premature termination codon and truncated MPO protein. Functional experiments further demonstrated that all four affected individuals showed MPO activity inversely correlating with the activity of NE, CTSG and PR3, three serine proteases that cleave IL-36 precursors into pro-inflammatory forms. These data strongly suggest that MPO deficiency may be involved in the pathogenesis of GPP through regulating the activity of neutrophil and monocytic proteases, and in turn activating pro-inflammatory IL-36 signals. In addition, MPO deficiency caused the reduction of neutrophil extracellular traps (NET) formation in PMA-induced pathway and impaired phagocytosis of neutrophils by monocytes, thereby tolerating the persistence of unfavorable neutrophils and blocking resolution of skin inflammation. Notably, dosage of mutant alleles of MPO gene in individuals affected by GPP also correlated with the age of onset, which is similar to the genotype-phenotype correlation of IL36RN gene and further validates the genetic correlation of GPP. Thus, the novel findings that MPO gene is a pathogenic gene for GPP provide new insights for the elucidation of GPP pathogenesis, even if the in-depth pathogenic mechanism and new pathogenic variants of MPO gene remain to be identified.

3. IL-1/IL-36-chemokine-neutrophil axis is a potent driver of disease pathology in GPP

Among the mutations identified in the disease-causing genes IL36RN, CARD14, APIS3 and the newly identified MPO in GPP patients, those present in IL36RN play a pathogenic dominant role. In addition, the IL-1/IL-36-chemokine-neutrophil axis is considered a core pathogenic molecular pathway. In the present study, we found that all four disease-causing genes share some common pathogenic molecular pathways. IL36RN, CARD14 and APIS3 gene mutations can activate pro-inflammatory signaling pathways via NF-kB, and further result in an increased expression of CXCL1-3, IL-1, IL-8, and even IL-36 pro-inflammatory cytokines (18-21). In addition, MPO gene deficiency also promotes the activation of IL-36 signals by regulating the activity of NE, CTSG and PR3 serine proteases (Fig. 2) (59).

Recently, the new disease concept of autoinflammatory keratinization disease (AiKD) has been designated to comprise inflammatory keratinization disorders with genetic autoinflammatory pathomechanisms (65). GPP associated with IL36RN and CARD14 mutations are included and early-onset GPP is considered a typical one (66,67). Thus, initial genetic causative factors related to the hyperactivation of innate immunity or autoinflammation play dominant roles in the pathogenesis of GPP (65-68). Unanimously, transcriptomic analysis revealed that GPP patients share with patients affected by plaque-type psoriasis the expression of common molecules and pathways related to neutrophil chemotaxis; however, the pathomechanisms operating in GPP patients are more related to innate immunity inflammation (29,69) and those present in plaque psoriasis are more dependent on adaptive immunity responses (29). Thus, it is believed that the IL-1/IL-36 inflammatory axis is central to the disease pathology in GPP, whereas the TNF-α/IL-17/IL-23 axis appears to plays a more important role in plaque psoriasis (31,70,71). A gene expression study found that IL-17, TNF-α, IL-1, IL-36 and interferons (IFNs) were overexpressed both in GPP and plaque psoriasis lesions, whereas GPP lesions exhibited a higher mRNA level of IL-1 and IL-36 and lower of IL-17 and IFN-γ, as compared with plaque psoriasis lesions (29). Consequently, a high expression of CXCL1, CXCL2, CXCL8 and IL-8 neutrophil chemoattractants is observed in GPP lesions. Liang et al (69) further demonstrated that GPP, PPP and AGEP pustular skin disorders have a common molecular basis responsible for neutrophil chemotaxis. Of note, overexpression of two inflammatory-related proteins, namely six-transmembrane epithelial antigens of prostate1 and 4 (STEAP1 and STEAP4), was revealed in the three pustular skin disorders. Those molecules promoted neutrophil-rich, pro-inflammatory responses in the skin by favoring induction of IL-1/IL-36 cytokines and CXCL1 and IL-8 neutrophil chemokines in the skin microenvironment. By contrast, STEAP1 and STEAP4 are not upregulated in plaque psoriasis, consistent with a weak induction of neutrophil-activating cytokines in PV. This confirms that neutrophil recruitment is preferentially active in pustular psoriasis, which is distinct from plaque-type psoriasis mostly characterized by IL-17/IL-23 immunity responses (Boehner et al, Mudigonda et al, Coimbra et al, Grine et al, Fanoni et al) (14,72-75). Thus, IL-1/IL-36 inflammatory axis can be considered a pivotal pathogenic pathway typically activated in GPP. Its targeting by novel biological drugs potentially represent an effective therapeutic strategy for GPP treatment.

4. Novel biologics treatment for GPP based on pathoimmunology

At present, no standard guidelines for the treatment of GPP have been established, and no specific therapeutic agents for GPP have been approved in the United States or Europe. GPP management currently refers to guidelines for psoriasis vulgaris. However, new biologics targeting cytokines, including TNF-α/IL-17/IL-23 and IL-1/IL-36 axis inhibitors, that are related to pathological immunology bring bright prospects for the treatment of GPP. The most relevant biological treatments have been summarized in Table IV. While TNF-α/IL-17/IL-23 axis is preferentially blocked in plaque psoriasis, IL-1/IL-36-chemokine-neutrophil axis appears to be a more promising therapeutic target in GPP.

IL-1 targeting with biologics has been previously performed in GPP patients using the IL-1α receptor antagonist (IL-1α-RA) anakinra and the IL-1β monoclonal antibodies gevokizumab and canakinumab. Hüffmeier et al (76) reported successful treatment with anakinra, produced by genetic recombination technology,
Table IV. Summary of biologics treatment for GPP.

| Type               | Drug                        | Properties                                    | Therapeutic target | IL36RN mutations of patients enrolled (Refs.) |
|--------------------|-----------------------------|-----------------------------------------------|--------------------|-----------------------------------------------|
| TNF-α inhibitors   | Etanercept                  | Recombinant DNA-derived TNF-α                 | TNF-α              | c.80T>C (80-84)                               |
|                    | Infliximab                  | TNF receptor-IgG fusion protein               | TNF-α              | c.115+6T>C (51,82,83, 85,86)                  |
|                    | Adalimumab                  | Fully human monoclonal antibody              | TNF-α              | N/A (82,83,87, 88)                            |
| IL-17 inhibitors   | Ixekizumab                  | Monoclonal antibody                           | IL-17A             | N/A (89-91)                                   |
|                    | Secukinumab                 | Monoclonal antibody                           | IL-17A             | c.115+6T>C (90,92-94)                         |
|                    | Brodalumab                  | Monoclonal antibody                           | IL-17R             | N/A (95)                                      |
| IL-23 inhibitors   | Ustekinumab                 | Monoclonal antibody                           | IL-12/23 p40       | c.227C>T (96,97)                              |
| IL-1R antagonist   | Anakinra                    | Human recombinant IL-1RA protein             | IL-1R              | c.142C>T, C.338C>T (76,98)                    |
| IL-1β antagonists  | Gevokizumab                 | Monoclonal antibody                           | IL-1β              | N/A (77)                                      |
|                    | Canakinumab                 | Monoclonal antibody                           | IL-1β              | N/A (78)                                      |
| IL-36R antagonist  | BI655130                    | Monoclonal antibody                           | IL-36R             | c.80T>C, c.115+6T>C (79)                      |

N/A, not applicable.

Figure 2. Pathways and processes of inflammatory responses induced by IL36RN, CARD14, AP1S3 and MPO genes. Loss-of-function mutations in both IL36RN and MPO genes cause upregulation of IL-36 signaling, the former result in the inability of IL-36Ra to antagonize and limit the pro-inflammatory effects of IL-36, the latter upregulate the activity of NE, CTSG and PR3, three serine proteases that cleave IL-36 precursors into pro-inflammatory forms. Upregulated IL-36 signaling further activates the downstream pro-inflammatory NF-κB pathway and are involved in the processes of inflammatory responses. Red or black arrows, secretion or activation; ↓, inhibition; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; LOFM, loss-of-function mutations; GOFM, gain-of-function mutations; STEAP1, six-transmembrane epithelial antigens of prostate 1; STEAP4, six-transmembrane epithelial antigens of prostate 4.
in a patient with GPP carrying the mutation of \textit{IL36RN} gene. Gevokizumab is an effective monoclonal antibody blocking the pro-inflammatory cytokine \textit{IL}-1 and its signal transduction in inflammatory cells. Mansouri \textit{et al} (77) reported the 79 and 65\% reduction in Psoriasis Activity and Severity Index (PASI) score at weeks 4 and 12 after treatment with gevokizumab in two patients with severe, recalcitrant GPP. Skendros \textit{et al} (78) reported a case of abrupt and severe form of GPP with hypereosinophilia and cholestatic hepatitis, completely cleared after treatment with canakinumab, leading to anakinra discontinuation for persistent hypersensitivity skin reactions. The new monoclonal antibody BI655130 targeting \textit{IL}-36 receptor can effectively block the \textit{IL}-36 signaling pathway and alleviate inflammatory response in GPP patients. A study on the treatment of GPP with BI655130 showed that all 7 GPP patients carrying homozygous \textit{IL36RN} mutation (n=3), or heterozygous mutation in \textit{CARD14} (n=1) or wild-type alleles (n=4) significantly responded to BI655130 after 4-week therapy (79). The finding suggested that \textit{IL}-36R inhibition with a single dose of BI655130 can effectively alleviate the severity of GPP regardless of the presence of the disease-causing gene mutation and has great potential for future clinical treatment of GPP. No serious adverse reactions and recurrences related to therapy were reported in the abovementioned studies. However, since clinical studies are very limited and current data mainly derive from case reports or small single-arm studies, further clinical investigations on larger populations are required in order to determine the clinical efficacy, duration of effect, and adverse events associated with the drug.

5. Conclusion and perspectives

The advances in our understanding of the genetic variation underlying GPP has provided an outstanding framework for basic research on the pathogenesis and treatment of GPP. These advances have suggested several new theories while simultaneously generating significant challenges. Evidence on the correlation between genotype and clinical phenotype of GPP characterized by various studies suggested that GPP is a heterogeneous disease with distinct clinical manifestations and genetic characteristics, and requires a separate diagnosis and treatment. Previous studies reported that some GPP patients carry two or three disease-causing gene variants or multiple mutations in one disease-causing gene (17,22,23,59), and some healthy subjects who carry the homozygous mutation of c.115+6T>C in \textit{IL36RN} gene, which theoretically leads to the complete loss of \textit{IL36RN} function, did not develop GPP until adulthood (15). Thus, it is suggested that the genetic basis for the onset of GPP is an oligogenic rather than a purely monogenic inheritance. The pathogenic variants in all four genes found in patients with GPP can work together and promote skin inflammation by increasing the production of pro-inflammatory cytokines in keratinocytes, which ultimately shift the balance towards substantial inflammation. Studies also found that large number of GPP patients did not carry any known genetic variations in \textit{IL36RN}, \textit{CARD14}, \textit{AP1S3} and \textit{MPO} genes (23), which suggests that some novel variants located in introns or regulatory regions and other genetic factors outside these four genes are expected to contribute to the pathogenesis of the GPP. Therefore, further screening and validating more pathogenic variants or novel pathogenic genes may provide key insights into disease pathogenesis, as well as the corresponding treatment and prevention strategies of GPP. We found that the function of numerous possible pathogenic variants reported remains to be validated. Therefore, functional research models \textit{in vitro} and \textit{in vivo} are required to be established for further elucidating the pathological mechanism. Although great progress in therapy of GPP with biologics has been made, current treatment studies are limited owing to a lack of data from controls and the number of patient cohorts due to GPP rarity. Thus, it is necessary to expand the patient cohorts from different countries and ethnicities to provide more reliable data on long-term maintenance of safety, efficacy and the impact of withdrawal/re-treatment with new biologics.

**Acknowledgements**

The authors would like to express their gratitude to EditSprings (https://www.editsprings.com/) for the expert linguistic services provided.

**Funding**

This review is supported by the Sichuan Science and Technology Program (grant nos. 2019YFS0332, 2019YFS0038, and 2020YFQ0045).

**Availability of data and materials**

Not applicable.

**Authors’ contributions**

JZ and JL conceived and designed the review. JZ and QL conducted formal literature search and analysis. QL, YC and XW contributed to the raw data reviewing. JZ was involved in the original draft preparation. JL was involved in the writing and review of the manuscript. All the authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Köks S, Kingo K, Smith C, Barker JN; ERASPEN Network: European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 31: 1792-1799, 2017.
2. Baker H and Ryan TJ: Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol 80: 771-793, 1968.
3. Ohkawara A, Yasuda H, Kobayashi H, Inaba Y, Ogawa H, Hashimoto I and Imamura S: Generalized pustular psoriasis in Japan: Two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol 76: 68-71, 1996.
13. Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Ito T, Takahashi H, Kawada A, Iizuka H and Nakagawa H; 4. Augey F, Renaudier P and Nicolas JF: Generalized pustular psoriasis. J Invest Dermatol 133: 1366‑1369, 2013.

15. Li M, Han J, Lu Z, Li H, Zhu K, Cheng R, Jiao Q, Zhang C, Zhu C, Zhang Y, et al: Prevalent and rare mutations in IL‑36RN gene in Chinese patients with generalized pustular psoriasis and psoriasis vulgaris. J Invest Dermatol 133: 2637‑2639, 2013.

16. Takahashi H, Nakamura K, Kaneko F, Nakagawa H and Iizuka H; 6. Takahashi H, Nakamura K, Kaneko F, Nakagawa H and Iizuka H; 7. Nakamura K, Nakagawa H and Iizuka H; 8. Talaee R, Hajheydari Z, Moghaddam AY, Moraveji SA and Wu W, Pan F, Mockenhaupt M, Wilsmann‑Theis D, Oji V, Gkogkolou P, Löhr S, Schulz P, Körber A, Prinz JC, Renner R, Schäkel K, et al: IL‑1 and IL‑36 are dominant cytokines in generalized pustular psoriasis. Acta Derm Venereol 98: 5‑13, 2018.

21. Vergnano M, Mockenhaupt M, Brir VA, Garcia‑Gal Legos K, Mahil SK, Twelves S, Farkas K, Wilson M, Ryan C, Duan S, Helms CA, Liu Y, Seyger MM, Kido‑Nakahara M, Kadono T, Harms PW and Gudjonsson JE: IL‑1 and IL‑36 signalling in plaque psoriasis and pustular psoriasis. J Invest Dermatol 136: 2251‑2259, 2016.

22. Mahil SK, Tewels S, Farkas K, Setta‑Kaffetzi N, Burden AD, Gach JE, Ireland AD, Képíro L, Mckenhook M, Oon HH, et al: IL1P3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up‑regulating IL‑18 production. J Invest Dermatol 135: 2438‑2444, 2009.

23. Mössner R, Wilsmann‑Theis D, Oji V, Gkogkolou P, Löhr S, Seyger MM, Kido‑Nakahara M, Kadono T, Harms PW and Gudjonsson JE: IL‑1 and IL‑36 are dominant cytokines in generalized pustular psoriasis. Acta Derm Venereol 98: 5‑13, 2018.

24. Sugiura K, Muto M and Akiyama M: CARD14 c.526G>CMutations in CARD14 are predisposing factors for generalized pustular psoriasis (GPP) with psoriasis vulgaris but not for GPP alone in a Japanese population. Br J Dermatol 170: 108‑109, 2014.

30. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Zlotogorski A and Molho‑Pessach V: AP1S3 mutations are associated with pustular psoriasis‑a model disease for specific targeted immunotherapy, IMID 2009, Vienna, 2009.

31. Reddy S, Jia S, Geoffrey R, Loriger R, Suchi M, Broeckel U, Messori A, Aerts M, Augey F, Renaudier P and Nicolas JF: Prevalent and rare mutations in IL‑36RN gene in Chinese patients with generalized pustular psoriasis and psoriasis vulgaris. J Invest Dermatol 133: 2637‑2639, 2013.

32. Cowen EW and Goldbach‑Mansky R: DIRA, DITRA, and new autoinflammatory phenotype of generalized pustular psoriasis. J Clin Immunol 34: 1755‑1757, 2014.

33. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, Ryan C, Seyger MM, Kido‑Nakahara M, Kadono T, Harms PW and Gudjonsson JE: IL‑1 and IL‑36 signalling in plaque psoriasis and pustular psoriasis. J Invest Dermatol 136: 2251‑2259, 2016.

34. Reddy S, Jia S, Geoffrey R, Loriger R, Suchi M, Broeckel U, Messori A, Aerts M, Augey F, Renaudier P and Nicolas JF: Prevalent and rare mutations in IL‑36RN gene in Chinese patients with generalized pustular psoriasis and psoriasis vulgaris. J Invest Dermatol 133: 2637‑2639, 2013.

35. Sugiura K, Takeichi T, Kono M, Ogawa Y, Shimoyama Y, Muro Y and Akiyama M: A novel IL36RN/IL1F5 homozygous nonsense mutation, p.Arg10X, in a Japanese patient with adult‑onset generalized pustular psoriasis. Br J Dermatol 176: 699‑701, 2012.

36. Kanazawa N, Nakamura T, Mikita N and Furukawa F: Novel IL36RN mutation in a Japanese case of early onset generalized pustular psoriasis. J Dermatol 40: 749‑751, 2013.

37. Farooq M, Nakai H, Fujikawa H, Matsuyama A, Kariya N, Aizawa A, Fujihara W, Ito M and Shimomura Y: Mutation of the interleukin‑1‑receptor antagonist. N Engl J Med 360: 2426‑2437, 2009.

38. Seyger MM, Kido‑Nakahara M, Kadono T, Harms PW and Gudjonsson JE: IL‑1 and IL‑36 signalling in plaque psoriasis and pustular psoriasis. J Invest Dermatol 136: 2251‑2259, 2016.

39. Setta‑Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon SE, Allen MA, Burden AD, Griffiths CE, Seger MM, et al: Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis‑associated pustular phenotypes. J Invest Dermatol 133: 1366‑1369, 2013.

40. Sugiura K, Nakasuka A, Kono M and Akiyama M: Impaired keratinocyte interleukin‑1 pathway with IL36RN mutations in a Chinese patient: A founder haplotype of c.115+6T>C in East Asia. J Dermatol Sci 79: 319‑320, 2015.

41. Shiratori T, Fukai K, Yasumizu M, Taguchi R, Tsuruta D, Abe Y, Suzuki M, Hori K, Hozumi Y and Suzuki T: IL36RN gene analysis of pediatric patients with GPP alone and GPP with secondary impetigo herpetiformis. J Dermatol Sci 79: 319‑320, 2015.

42. Komine M, Kamiya K, Tsuda H, Maekawa T, Murata S, Ueda Y, Komine M, Kamiya K, Tsuda H, Maekawa T, Murata S, Ueda Y, et al: Significant risk factor for generalized pustular psoriasis with psoriasis vulgaris in the Japanese cohort. J Invest Dermatol 134: 1755‑1757, 2014.
56. Jordan CT, Cao L, Roberson ED, Duan S, Helms CA, Nair RP, Marchetti C, Patriarca P, Solero GP, Baralle FE and Romano M: Genetic studies on myeloperoxidase deficiency in Italy. Jpn J Infect Dis 57: S10-S12, 2004.

57. Marchetti C, Patriarca P, Solero GP, Baralle FE and Romano M: Genetic characterization of myeloperoxidase deficiency in Italy. Hum Mutat 23: 496-505, 2004.

58. Berki DM, Liu L, Choon SE, David Burden A, Griffiths CEM, Ellingford JM, Black GC, Clayton TH, Judge M, Griffiths CE: Genetic characterization of myeloperoxidase deficiency in Italy. Hum Mutat 23: 496-505, 2004.

59. De Argila D, Dominguez JL, Lopez-Esteban JL and Iglesias L: Pustular psoriasis in a patient with myeloperoxidase deficiency. Dermatology 193: 270, 1996.

60. Stendahl O, Coble BL, Dahlgren C, Hed J and Molin L: Myeloperoxidase modulates the phagocytic activity of polymorphonuclear neutrophil leukocytes. Studies with cells from a myeloperoxidase-deficient patient. J Clin Invest 73: 366-373, 1984.

61. Kizaki M, Miller CW, Selsted ME and Koeffler HP: Myeloperoxidase (MPO) gene mutation in hereditary MPO deficiency. Blood 83: 1935-1940, 1994.

62. Marchetti C, Patriarca P, Solero GP, Baralle FE and Romano M: Genetic studies on myeloperoxidase deficiency in Italy. Jpn J Infect Dis 57: S10-S12, 2004.

63. Marchetti C, Patriarca P, Solero GP, Baralle FE and Romano M: Genetic characterization of myeloperoxidase deficiency in Italy. Hum Mutat 23: 496-505, 2004.
86. Pan J, Qiu L, Xiao T and Chen HD: Juvenile generalized pustular psoriasis with IL36RN mutation treated with short-term infliximab. Dermatol Ther 29: 164-167, 2016.

87. Morita A, Yamazaki F, Matsuyama T, Takahashi K, Arai S, Asahina H, Imafuku S, Nakagawa H, Hasegawa Y, Williams D, et al: Adalimumab treatment in Japanese patients with generalized pustular psoriasis: Results of an open-label phase 3 study. J Dermatol 45: 1371-1380, 2018.

88. Matsumoto A, Komine M, Karakawa M, Kishimoto M and Ohtsuki M: Adalimumab administration after infliximab therapy is a successful treatment strategy for generalized pustular psoriasis. J Dermatol 44: 202-204, 2017.

89. Egawa G, Honda T and Kabashima K: Long-term efficacy of ixekizumab in erythrodermic and generalized pustular psoriasis patients. J Eur Acad Dermatol Venereol 33: 259, 2019.

90. Wilsmann-Theis D, Schnell LM, Ralser-Isselstein V, Bieber T, Schön MP, Höffmeier U and Mössner R: Successful treatment with interleukin-17A antagonists of generalized pustular psoriasis in patients without IL36RN mutations. J Dermatol 45: 850-854, 2018.

91. Okubo Y, Mabuchi T, Iwatsuki K, Elmaraghy H, Torisu-Itakura H, Morisaki Y and Nakajo K: Long-term efficacy and safety of ixekizumab in Japanese patients with erythrodermic or generalized pustular psoriasis: Subgroup analyses of an open-label, phase 3 study (UNCOVER-J). J Eur Acad Dermatol Venereol 33: 325-332, 2019.

92. Ho PH and Tsai TF: Successful treatment of refractory juvenile generalized pustular psoriasis with secukinumab monotherapy: A case report and review of published work. J Dermatol 45: 1353-1356, 2018.

93. Imafuku S, Honma M, Okubo Y, Komine M, Ohtsuki M, Morita A, Seko N, Kawashima N, Ito S, Shima T and Nakagawa H: Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: A 52-week analysis from phase III open-label multicenter Japanese study. J Dermatol 43: 1011-1017, 2016.

94. Gabeff R, Safar R, Leducq S, Maruani A, Sarrabay G, Touitou I and Samimi M: Successful therapy with secukinumab in a patient with generalized pustular psoriasis carrying homozygous IL36RN p.His32Arg mutation. Int J Dermatol 58: e16-e17, 2019.

95. Yasumaki K, Nakagawa H, Kubo Y and Ootaki K: Japanese Brodalumab Study Group: Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: Results from a 52-week, open-label study. Br J Dermatol 176: 741-751, 2017.

96. Storan ER, O’Gorman SM and Markham T: Generalized pustular psoriasis treated with ustekinumab. Clin Exp Dermatol 41: 689-690, 2016.

97. Arakawa A, Ruzicka T and Prinz JC: Therapeutic efficacy of interleukin 12/interleukin 23 blockade in generalized pustular psoriasis regardless of IL36RN mutation status. JAMA Dermatol 152: 825-828, 2016.

98. Viguier M, Guigue P, Pages C, Smahi A and Bachelez H: Successful treatment of generalized pustular psoriasis with the interleukin-1-receptor antagonist Anakinra: Lack of correlation with IL1RN mutations. Ann Intern Med 153: 66-67, 2010.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.