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

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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 erythematous, 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, AP1S3* 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.

Contents

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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 erythematous eruptions with neutrophil-filled pustules1 (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*, *AP1S3,* 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*, *AP1S3* 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 *AP1S3* 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 (NF-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 thirty-six-receptor antagonist (DITRA) (18,28,32). Notably, patients with DITRA primarily involved the skin and presented with high-grade fever and general malaise during an attack, in contrast to 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.Arg10ArgfsX1), 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.Arg10ArgfsX1) (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

Table I. Mutations of *IL36RN* gene and related characteristics in GPP patients.

Nucleotide variations	Amino acid variations	Variant type	Status of the mutations	Origin	Protein expression *in vitro*	Inflammation inhibition *in vitro*	(Refs.)
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	None	Impaired	(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	CHet	German	None	Impaired	(23,39,47)
c.304C>T	p.Arg102Trp	Missense	Hom/CHet/ Het	British/ Turkish/ East Asian	Unchanged	Unchanged	(22,38,39, 42)
c.305G>A	p.Arg102Gln	Missense	Het	Chinese	Not reported	Not reported	(15)
c.308G>A	p.Arg103Gln	Missense	Het	German	Not reported	Not reported	(23)
c.334G>A	p.Glu112Lys	Missense	CHet	Chinese	Not reported	Not reported	(49)
c.338C>T	p.Ser113Leu	Missense	Hom/CHet/ Het	British/ German/ Iraqi/ Swiss/ Russian	Reduced	Reduced	(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	CHet deletion	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.

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

Studies, year	Origin	No. of patients enrolled	Correlation between *IL36RN* mutations and clinical presentations				(Refs.)
			Low prevalence of PV	Early age of onset	Severe inflammation	High recurrence rate	
Sugiura *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.

GPP alone was much higher than that observed in patients with both GPP and PV forms, Sugiura *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).

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-κB 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-κB 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-κB, 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-κB 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, Sugiura *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, Sugiura *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 control (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

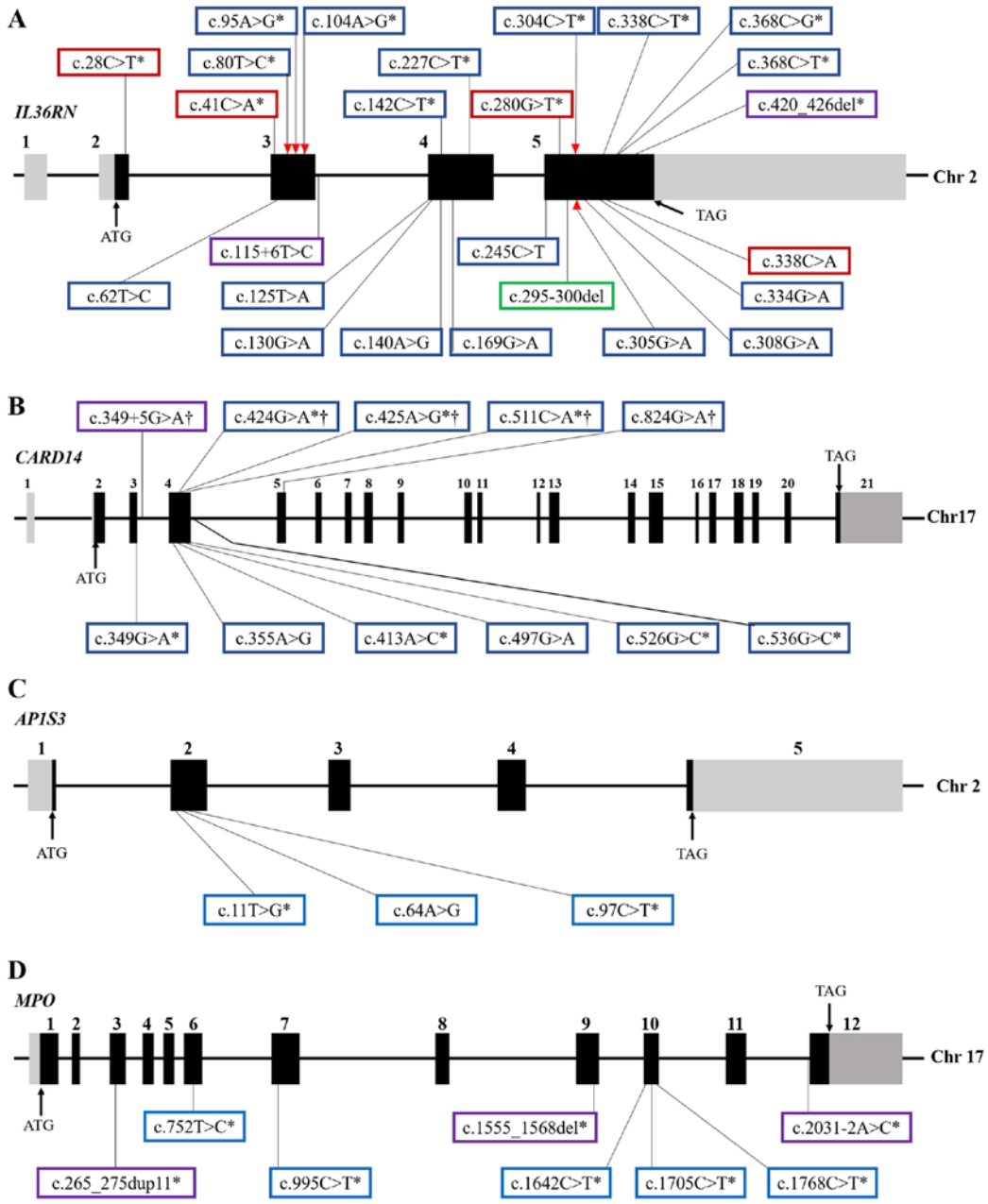

Figure 1. Genomic structure of GPP-related genes and location of the identified variants. Exons and relative non-coding introns of (A) *IL36RN*, (B) *CARD14*, (C) *AP1S3* and (D) *MPO* genes were shown by solid black and gray boxes, respectively. Blue, red, purple and green boxes represent, respectively, 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.

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 AP1S3. *AP1S3* 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 *AP1S3* gene are relevant in GPP. In 2014, Setta-Kaffetzi *et al* (20) identified heterozygosity for the c.11T>G (p.Phe4Cys) and c.97C>T (p.Arg33Trp) missense mutations in *AP1S3* 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).

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.Asp176His	Missense	Het	Japanese/ Chinese	2.78	(22,24,25, 56,58)
c.536G>A	p.Arg179His	Missense	Het	German	1.38 (2.19 with TNF-α stimulation)	(23,56)
c.424G>A†	p.Glu142Lys	Missense	Het	Not reported	4.03	(56)
c.425A>G†	p.Glu142Gly	Missense	Het	Not reported	5	(56)
c.511C>A†	p.His171Asn	Missense	Het	Not reported	0.68 (5.95 with TNF-α stimulation)	(56)
c.824G>A†	p.Arg275His	Missense	Het	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-ß1 (IFNB1) following induction with polyinosinic-polycytidylic acid [poly(I:C)], an agonist of TLR3 involved in responses to viral infections. Thus, Setta-Kaffetzi *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 was identified in a daughter of a consanguineous marriage (23). All these subjects carried additional homozygous or compound-heterozygous *IL36RN* mutations, as shown in the study of Mössner *et al* (23). Similarly, Twelves *et al* (22) found that 8 out of 251 GPP cases carry c.11T>G (4 cases) or c.97C>T (4 cases) heterozygous mutations in the *AP1S3* gene, with two carriers of c.11T>G mutation in *AP1S3* gene also harboring the known pathogenic *IL36RN* variants. Of note, *AP1S3* pathogenic variants are mainly found in Europeans and rarely in East Asians, and variant frequency of *AP1S3* in GPP patients of European descent is 10.8% (4/37).

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

(p.Ser94Alafs*24), c.2031-2A>C, c.1768C>T (p.Arg590Cys) homozygous variants, the c.995C>T (p.Ala332Val) and c.2031-2A>C (p.Phe678*) compound heterozygous variants and the c.752T>C (p. Met251Thr), c.995C>T (p.Ala332Val), c.2031-2A>C, c.1705C>T, c.1642C>T (p.Arg548Trp), and 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.995C>T and c.752T>C) reduced MPO activity in HEK cells at different extent (Fig. 1D). While the 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, AP1S3* 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 *AP1S3* gene mutations can activate pro-inflammatory signaling pathways via NF-κB, 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-1-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 receptor-IgG fusion protein	TNF-α	c.80T>C	(80-84)
	Infliximab	Chimeric monoclonal antibody	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.

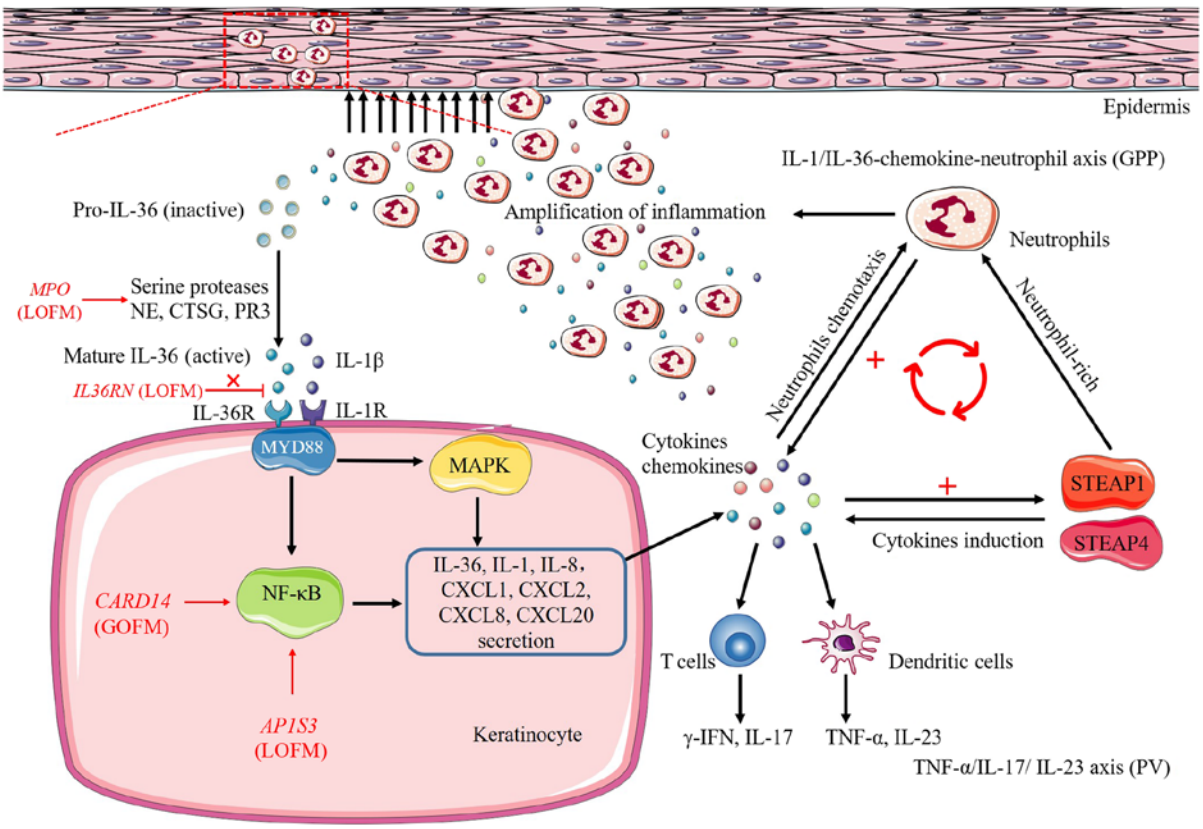

Figure 2. Pathways and processes of inflammatory responses induced by *IL36RN*, *CARD14*, *AP1S3* and *MPO* genes. Loss-of-function mutations in both *IL36RN* and *MPO* genes cause upregulation of IL-36 signaling, the former result in the inability of IL-36Ra to antagonize and limit the pro-inflammatory 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 and MAPK pathways by binding to IL-36 receptor, further leading to secretion of chemokines/cytokines, IL-36, IL-1, IL-8, CXCL1, CXCL2, CXCL8, CXCL20, from the keratinocyte and resulting in the activation of neutrophils, T cells and dendritic cells. Secretion of cytokines also promotes neutrophil-rich, cytokines induction, thereby amplifying the pro-inflammatory responses in the skin by two inflammatory-related proteins STEAP1 and STEAP4, ultimately forming a vicious cycle of enhancing inflammation. In addition, *CARD14* gain-of-function mutations and *AP1S3* loss-of-function mutations hyperactivate 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 *IL36RN* gene. Gevokizumab is an effective monoclonal antibody blocking the pro-inflammatory cytokine IL-1β and its signal transduction in inflammatory cells. Mansouri *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 *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 IL-36 receptor can effectively block the 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 *IL36RN* mutation (n=3), or heterozygous mutation in *CARD14* (n=1) or wild-type alleles (n=4) significantly responded to BI655130 after 4-week therapy (79). The finding suggested that 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 *IL36RN* gene, which theoretically leads to the complete loss of 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 *IL36RN*, *CARD14, AP1S3* and *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 *in vitro* and *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.

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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.

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