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Update on the aetiology and mechanisms of generalized pustular psoriasis

Generalized pustular psoriasis (GPP) is a chronic disease characterized by non-bacterial pustules. Variants in several genes, such as *IL36RN*, *AP1S3*, and *CARD14*, are involved in the pathogenesis of GPP. The prevalence of different gene variants varies among ethnicities, and some variants are related to concurrent psoriasis vulgaris or age at onset. Flares can be triggered by medications (most commonly corticosteroids), infections (possibly due to Toll-like receptor [TLR] and antimicrobial peptides), pregnancy (the onset of GPP has been attributed to endocrine abnormalities such as hypoparathyroidism and hypocalcaemia), hypocalcaemia (presumably due to low levels of calcium and vitamin D regulating the proliferation and differentiation of keratinocytes), and other factors including stress and sun exposure. The mechanisms of pustule formation involve: 1) the LL37/TLR pathway, in which LL37 acts as an alarmin, interacting with TLR and activating the NF-κB and MAPK pathways; 2) the balance between calcium and 1,25(OH)2D levels, and 3) neutrophils and the complement system.

Key words: pustular psoriasis, aetiology, toll-like receptor, antimicrobial peptide, vitamin D

Pustular psoriasis is an uncommon form of psoriasis that manifests as acute or subacute sterile pustules appearing on areas of erythema, accompanied by moderate to severe systemic inflammatory symptoms such as fever, malaise, asthenia, myalgia, and arthralgia. Generalized pustular psoriasis (GPP) can be divided into pso + GPP, in which the patient is diagnosed with psoriasis vulgaris before the onset of GPP, and pso-GPP, in which no psoriasis vulgaris is observed prior to the onset of GPP [1]. Despite the significant clinical, social, and economic burden imposed by GPP, this condition is poorly understood and under-studied. Because GPP is a chronic relapsing disease, gaining a better understanding of its aetiology and pathogenesis would facilitate disease prevention.

The aetiology of pustular psoriasis is poorly understood. GPP seems to occur as the result of variations in several genes such as the gene encoding the interleukin (IL)-36 receptor antagonist (*IL-36RN*), caspase recruitment domain family member 14 (*CARD14*), and adaptor-related protein complex 1 subunit sigma 3 (*AP1S3*). While the prevalence of these variants varies depending on ethnicity, recent reports indicate that up to 60.5%, 5.9%, and 10.8% of patients with GPP have mutations/variations in *IL36RN*, *CARD14*, and *AP1S3*, respectively [2]. In addition to the contribution of these gene variants, GPP flare-ups tend to be triggered by specific factors. In several retrospective analyses [1, 3-5], the most commonly reported precipitating factors were: the withdrawal of medications (approximately 30–50% of cases); infections, particularly upper respiratory tract infections (approximately 20%); pregnancy (60% of pregnant GPP women and 20-40% of GPP cases as a whole); and others, including hypocalcaemia, stress, sun exposure, and seasonal variation [3]. Different subtypes of GPP have distinct clinical features and triggers. Medications (75%), including steroids (15–28%), trigger flares more frequently in pso + GPP patients, whereas in pso-GPP patients, the most common precipitating factors are respiratory tract infections (42%) and pregnancy (35%) [6]. In this paper, we review the aetiology and mechanisms of GPP.

Predisposing factors of generalized pustular psoriasis

Gene variants

IL-36RN

A recent study showed that *IL36RN* alleles demonstrate a dose-dependent effect on the age at onset in all forms of pustular psoriasis, particularly in the pso-GPP population; this phenomenon has been observed in China, Japan, and Germany [6-8]. *IL36RN* encodes the IL-36 receptor antagonist (IL-36Ra), an anti-inflammatory cytokine. IL-36Ra malfunction leads to upregulation of IL-1 family cytokines, resulting in the unregulated secretion of inflammatory cytokines, and hence GPP. Worldwide, between 46.15% and 81.82% of patients with GPP alone have *IL36RN* variants [8, 9], compared with 10% to 37.78% of patients with pso + GPP [8, 10]. The prevalence of different variants varies in different ethnic groups [11, 12]. GPP-related *IL36RN* alleles are most prevalent in patients of European (34.7%) and East Asian (28.8%) descent. In

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Table 1. Different variants of genes and related characteristics in generalized pustular psoriasis patients.

Gene	Nucleotide variations	Amino acid variations	Geographic origin	PolyPhen2 predicted effect on protein function	References
IL36RN	c.308C > T	p.Ser113Leu	European	Possibly damaging	Setta-Kaffetzi et al., 2013
	c.142C > T	p.Arg48Trp	European	Probably damaging	Setta-Kaffetzi et al., 2013
	c.104A > G	p.Lys35Arg	European	Benign	Setta-Kaffetzi et al., 2013
	c.80T > C	p.Leu27Pro	African	Possibly damaging	Marrakchi et al., 2011
	c.115 + 6T > C	p.Arg10ArgfsX1	Asian	-	Li et al., 2013; Farooq et al., 2013
	c.227C > T	p.Pro76Leu	Asian	Probably damaging	Körber et al., 2013
	c.368C > G	p.Thr123Arg	Asian	Probably damaging	Farooq et al., 2013
	c.368C > T	p.Thr123Met	Asian	Probably damaging	Kanazawa et al., 2013[100]
	c.140A > G	p.Asn47Ser	Asian	Probably damaging	Li et al., 2013
	c.28C > T	p.Arg10X	Asian	Probably damaging	Farooq et al., 2013; Sugiura et al., 2012[101]
	c.95A > G	p.His32Arg	Asian	Benign	Körber et al., 2013
CAR14	c.413A > C	p.Glu138Ala	Asian	Probably damaging	Sugiura et al., 2014; Berki et al., 2015
	c.526G > C	p.Asp176His	Asian	Probably damaging	Sugiura et al., 2014; Berki et al., 2015
	c.355A > G	p.Met119Val	Asian	Benign	Qin et al., 2014
	c.497G > A	p.Arg166His	Asian	Benign	Qin et al., 2014
	c.2044C > T	p.Arg682Trp	Asian	Probably damaging	Qin et al., 2014
	c.536G > A	p.Arg179His	Caucasian/Asian	Probably damaging	Mössner et al., 2018
	c.1805C > T	p.Ser602Leu	European	Probably damaging	Ammar et al., 2016
AP1S3	c.11T > G	p.Phe4Cys	European	Probably damaging	Setta-Kaffetzi et al., 2014; Mahil et al., 2016
	c.97C >T	p.Arg33Trp	European	Probably damaging	Setta-Kaffetzi et al., 2014; Mahil et al., 2016

China, *IL36RN* variants have been reported in 46.8–60.5% of patients with GPP [6]. More than 20 *IL36RN* variants have been reported around the world, and patients can be homozygous, heterozygous, or compound heterozygous for these variants. Some variants are listed in *table 1*. Different ethnic groups exhibit distinct variant profiles. For example, variants c.115 + 6T > C and p.Pro76Leu are most commonly seen in Chinese, Japanese, and Malay patients with GPP, the most common variant in European patients is p.Ser113Leu, and p.Leu27Pro is mostly seen in African patients [13-17]. *IL36RN* variants are strongly linked with early onset of disease, geographic tongue (mucosae involvement), the formation of hyponychial pustules, GPP severity, acitretin therapeutic efficacy, or frequency of recurrence of disease, but not sex [18, 19]. Different variants may correspond to different phenotypes; for example, patients homozygous for the c.115 + 6T > C mutation are more likely to have severe phenotypes such as erythroderma and ulcerated pustules [18].

CARD14

Clinically, *CARD14* variants are observed in only a minority of GPP cases. *CARD14* encodes a scaffold protein that regulates the nuclear factor (NF)-κB signalling pathway, and is mainly expressed in epidermal keratinocytes. NF-κB is involved in the expression of genes encoding pro-inflammatory molecules such as TNF-α, IL-1, IL-6, and IL-8, and modulates keratinocyte differentiation and proliferation, thereby contributing to inflammatory responses within the epidermis [2]. The p.Gly117Ser, p.Glu138Ala, p.Glu142Lys, p.Glu142Gly, and p.Asp176His variants are associated with NF-κB activation and may be related to the pustular or plaque type of psoriasis [12, 20]. *CARD14* variants are commonly seen in Asian patients (including Japanese and Chinese patients), but rarely in European patients, and are more frequently seen in patients with pso + GPP (*table 1*) [12, 21-25].

Recently, we proposed the new disease concept of "autoinflammatory keratinization diseases" (AiKD), which encompasses inflammatory keratinizing diseases of the epidermis and upper dermis caused by hyperactivation of innate immunity due to genetic factors [26]. Primary, causative genetic factors associated with the hyperactivation of innate immunity (autoinflammation) play important roles in the pathogenesis of AiKD, which includes several diseases [27], such as GPP associated with *IL36RN* and *CARD14* mutations/variants [28].

AP1S3

Heterozygous *AP1S3* variants have also been found in patients with different subtypes of pustular psoriasis (mainly GPP and ACH). *AP1S3* encodes a member of the adaptor protein 1 (AP1) family that contributes to the deregulation of skin innate immune responses, such as the innate pattern recognition receptor Toll-like receptor 3 (TLR-3), resulting in a marked inhibition of downstream signalling

[29], and is also involved in protein trafficking in neutrophil activation [30]. *AP1S3* variants do not differ significantly across disease types and do not seem to influence the rate of concurrent PV or age at onset. The variants, p.Phe4Cys and p.Arg33Trp, have been detected in European patients with pustular psoriasis (*table 1*) [31]. Some patients carry multiple variants, *e.g.* variants in both *AP1S3* and *IL36RN* or in both *AP1S3* and *CARD14* [32].

Medications

A study revealed that in more than 74.1% of patients, pso + GPP was induced by the abrupt withdrawal of systemic and topical medicines [33], of which the most common were corticosteroids. Patients with psoriasis who received systemic glucocorticosteroid (GCS) medication at greater than Cushing dose (7.5 mg prednisolone equivalent per day) for more than 7–10 days may develop GPP during tapering or complete withdrawal of steroid dosage [34]. GCS-induced GPP is more intractable than normal GPP and is a potentially fatal condition, with unpredictable course and poor treatment response to conventional therapy. Hence, systemic GCSs should be avoided in patients with psoriasis unless vitally required. The withdrawal of cyclosporine has also been implicated in the development of pustular psoriasis [35].

Other drugs that can trigger GPP flare-ups include antibiotics such as the beta-lactam, amoxicillin [36], and antifungal agents such as terbinafine [37] and sulfonamides. However, this phenomenon is distinct from acute generalized exanthematous pustulosis, which also manifests as sudden eruption of multiple pustules and systemic symptoms after antibiotic administration. A past personal or family history of psoriasis can aid diagnosis. Pustular onset has also been linked to other medications such as cardiovascular drugs (ramipril, aspirin, beta-blockers), analgesics (morphine, NSAIDs), anticonvulsants (lithium), salicylates, potassium iodide, progestins, and hydroxychloroquine [38]. Topical use of calcipotriol and coal tar can also trigger GPP [39].

As a new emerging treatment modality, biological agents have been proven to be very effective in some refractory patients with psoriasis and other immune diseases, including biologics targeting tumour necrosis factor (TNF)-α and IL-6, -12/23, -17, and -23 [40]. However, despite the beneficial effects of these treatments, the cytokine imbalance caused by biologics promotes unchecked interferon-α activation, causing paradoxical adverse effects (PAEs). The most common PAEs in psoriasis treatment involve exacerbation of psoriasis or the development of new psoriasiform eruptions. Multiple studies have reported pustular formation or paradoxical pustular flares after the use of infliximab/adalimumab [41], ustekinumab [42], secukinumab [43], and rituximab [41].

Infections

The most common trigger among pso-GPP patients is infection, specifically upper respiratory tract infection [44]. The pathogens involved include streptococcal species, Staphylococcus aureus, Trichophyton rubrum, cytomegalovirus, varicella–zoster virus, and Epstein–Barr virus [38]. Administration of the H1N1 seasonal influenza vaccine has also been reported to trigger GPP [45]. Infection or epidermal injury results in the release of double-stranded RNA (ds-RNA) and the antimicrobial peptide LL37 from dead keratinocytes [46]. By further binding with TLR, especially TLR3, the LL37 complex triggers downstream NF-kB activation and production of pro-inflammatory cytokines and chemokines such as the IL-1/IL-36 axis, the IL-17/IL-23 axis, TNF-α, CXCL1, CXCL2, CXCL8, and CCL20 [47]. Many cell types participate in this process, including keratinocytes [48], dendritic cells [49], and neutrophils [50]. IL-6 exerts a significant influence on circulating neutrophils and promotes the production of secondary chemokines, such as IL-8, which are crucial to pustular formation [51].

Pregnancy

The GPP among pregnant women is called impetigo herpetiformis (IH) or pustular psoriasis of pregnancy [52]. This entity manifests as pustules studded on erythematous patches within intertriginous areas and the skin lesions gradually scatter to the whole body, accompanied by systemic symptoms. IH is a life-threatening condition for both the pregnant mother and the foetus.

Most IH patients have a positive personal or family history of psoriasis, nevertheless, there are still many cases without a known history [53]. Pregnancy-related endocrine abnormalities such as hypoparathyroidism, hypocalcaemia, diminished intestinal vitamin D absorption, and emotional stress have been suggested as potential triggers of the pustular formation [54, 55]. *IL36RN* variants may serve as predisposing factors in IH patients, and patients who are homozygous or heterozygous for *IL36RN* variants have been reported [56].

Primiparous women are at greater risk, and the symptoms often occur during the third trimester of pregnancy, but many reports have documented a similar episode in the first trimester [54] and there is an increased risk of more severe outbreaks in subsequent pregnancies that may present earlier. From an obstetric viewpoint, the complications most feared in IH are intrauterine growth retardation, stillbirth, and neonatal deaths secondary to congenital anomalies or placental insufficiency [57].

Hypocalcaemia

Hypocalcaemia in association with pustular psoriasis has been repeatedly reported in the literature. In many cases, hypocalcaemia is related to an iatrogenic cause; secondary or idiopathic hypoparathyroidism [58]. The pathogenic link between hypocalcaemia and pustular psoriasis is not entirely understood, but both *in vitro* and *in vivo* studies have revealed that calcium is a key regulator of keratinocyte proliferation and differentiation [59]. Vitamin D also plays a central role alongside thyroid function and calcium concentration. Altered vitamin D metabolism is seen in psoriasis patients [60]. What's more, as well as a trigger, the hypocalcaemia also occurs with GPP as a complication and is associated with hypoalbuminaemia and malabsorption [58]. With the level of calcium normalised, the pustules and erythroderma of GPP patients with hypocalcaemia resolve.

Potential mechanisms involved in pustule formation

Human cationic peptide-18 (hCAP-18/LL37) and Toll-like receptor

Endogenous antimicrobial peptides are an important part of natural immunity and play a key role in the host defence response [61]. Cathelicidin is a newly discovered antimicrobial peptide in mammals [62], and hCAP18 is the only member of the cathelicidin family that is found in humans. LL37 is derived from hCAP18 due to enzymatic cleavage in the human epidermis [63]. LL37 is widely distributed in the human body and has a broad spectrum of pro-inflammatory and antimicrobial effects [64], including: 1) direct interaction with invading micro-organisms, involving disintegration of the microbial cell wall, cell membrane, and/or lipid envelope [65]; 2) neutralization of endotoxin [66]; 3) acting as a chemoattractant for neutrophils and macrophages, resulting in the production and release of various chemokines and increased expression of some chemokine receptors [67, 68]; 4) promotion of mast cell degranulation, which releases histamine to improve vascular permeability and facilitates the formation of neutrophil extracellular traps [69]; and 5) triggering initial activation of T cells, particularly IL-17–producing T cells, T helper (Th)1 cells, and Th22 cells [70]. LL37 expression can be affected by several endogenous factors, including inflammatory cytokines, growth factors, and the active form of vitamin D [71]. High levels of LL37 have been associated with many inflammatory dermatological diseases such as rosacea and psoriasis [72]. Alarmins are endogenous, constitutively expressed, chemotactic, immune-activating proteins/peptides that are released as a result of degranulation, cell injury, or cell death, or in response to immune induction [73]. Injury and infection induce the epidermis to produce LL37 through TLR2 activation in keratinocytes [74]. As a result, LL37 is thought to be one of the alarmins involved in pustular psoriasis, for a variety of reasons. First, LL37 induces the expression of crucial cytokines, as shown by the increased expression of LL37-inducible genes (such as the IL-1 cluster genes, particularly IL36γ) in pustular psoriasis lesions. IL36γ production is activated by a G protein-coupled receptor–mediated signalling pathway and the mitogen-activated protein kinase (MAPK) signalling pathway [75]. Second, LL37 and IL36 act synergistically on keratinocytes to induce the expression of chemokines, such as CXCL1, CXCL8/IL8, CXCL10/IP-10 and CCL20/MIP3a, that are crucial factors for neutrophil aggregation [76]. Finally, LL37 amplifies the stimulation of IL-36 by inducing both ligands and their receptors in keratinocytes [75]. IL-36γ acts via the MAPK and NF-κB pathways to stimulate secretion of IL-8 by keratinocytes [77]. Furthermore, IL-8 and IL-36γ have been reported to be associated with pustule formation in generalized pustular psoriasis [78].

In addition to LL37, after the stimuli of injury or infection, keratinocytes also release self-DNA and self-RNA. LL37 enables plasmacytoid DC to recognize self-DNA through TLR9 [79] and form a complex, which further enables keratinocytes to induce more TLR9 and to react against TLR9 ligands [80]. The self-RNA–LL37 complex triggers the activation of classic myeloid DCs (mDCs) through TLR8 and activates TLR7, leading to the production of TNF-α, IL-6, and IFN-γ and the differentiation of mDCs and Th17 cells, activating γδT cells [81, 82]. In the infection-induced scenario, double-stranded RNA (dsRNA), a common by-product of viral infections, can be recognized by TLR3. After recognition, this activates NF-κB and three MAPKs (ERK, INK, and p38) through MyD88-dependent and independent pathways in macrophages to produce a series of cytokines and chemokines, such as TNF-α, IL-6, IFN-β and IL-1β [47]. Among them, IL-6 is a key downstream mediator acting together with IL-17 to induce excessive skin infiltration by neutrophils, resulting in intra-epidermal pustule formation [51].

LL37 may also act as a T-cell autoantigen in psoriasis and play an important role in both innate and adaptive immune cell activation. One study found that two thirds of patients with moderate-to-severe plaque psoriasis harbour CD4+ and/or CD8+ T cells specific for LL37, which could trigger activation of innate immune cells. LL37-specific T cells produce IFN-γ and infiltrate skin lesions and the peripheral blood. The presence of circulating LL37-specific T cells correlates significantly with disease activity, suggesting that they contribute to the pathogenesis of psoriasis [83].

Calcium and 1,25(OH)2D

Vitamin D, also known as the sunshine vitamin, has long been known to regulate calcium-phosphorous homeostasis and safeguards the integrity of the skeletal system. 1,25(OH)2D is the active form of vitamin D and accelerates the absorption of calcium, thereby promoting bone resorption and increasing the biological effect of parathyroid hormone, which ultimately elevates blood calcium levels [84]. Thus, serum vitamin D levels are tightly regulated by a feedback mechanism involving calcium, parathyroid hormone, and vitamin D itself [85]. Patients with psoriasis have been reported to have a disturbed calcium gradient, reduced calcium response, and reduced expression of all TRPC channels (calcium channels expressed on keratinocytes) in psoriatic keratinocytes [86], however, it is unclear whether these effects are a cause or consequence of GPP [87, 88].

Calcium may interact with the metabolic form of vitamin D (1,25(OH)2D) and influence the differentiation of keratinocytes. The mechanisms involved in the interaction are multifarious and include both genomic and non-genomic pathways [89, 90]. 1,25(OH)2D may suppress the differentiation of Th17 cells via regulating NF-κB activity [91]. 1,25(OH)2D may also modulate immune responses by regulating the differentiation of T helper (Th) 1, 9, 17 cells and by inducing the formation of antimicrobial peptides; such as cathelicidin peptides [92]. Injury or infection of the epidermis enhances TLR2 function and antimicrobial peptide expression through a vitamin D–dependent mechanism [74]. These mechanisms further connect the calcium and 1,25(OH)2D levels with hCAP-18/LL37 pathways, contributing to the pustule formation.

However, studies have shown that only 3.1% of pustular flares in patients with GPP are associated with hypocalcaemia [87], thus, some researchers believe that the hypocalcaemia seen in association with flares of pustular psoriasis is most often the result of hypoalbuminaemia [93].

Other possible factors

Transcriptome profiling technologies, such as microarray and RNA sequencing (RNA-seq), are valuable tools for deciphering the regulatory network underlying disease. Several studies have used RNA-seq to investigate patients with GPP. Johnson *et al*. compared skin lesions from patients with GPP to normal skin and plaque psoriasis (PV) skin lesions. The GPP transcriptome shares features with PV but is skewed towards innate immune inflammation. The transcripts up-regulated in GPP compared with normal skin mapped to 12 gene ontology (GO) Immune System Process terms: granulocyte chemotaxis, regulation of granulocyte chemotaxis, positive regulation of granulocyte chemotaxis, granulocyte migration, positive regulation of neutrophil migration, regulation of neutrophil chemotaxis, positive regulation of neutrophil chemotaxis, neutrophil chemotaxis, neutrophil migration, positive regulation of leukocytes, regulation of leukocyte chemotaxis, and positive regulation of leukocyte chemotaxis. Neutrophil and monocyte transcripts were enriched in GPP lesions compared with PV lesions. In addition, IL-17A, IL-1β, IL-36α, IL-36γ, IL-22, TNF-α, and IFN-γ tissue activity was higher in pustular lesions than in plaque biopsies, and a heightened IL-1/IL-36 cytokine axis, but less pronounced Th1/Th17 gene expression, was observed in GPP. Expression of the neutrophil chemokines, CXCL1, CXCL2, and CXCL8 (IL-8), was strongly enhanced in GPP, which was attributed to neutrophilic skin infiltration and the development of pustules [7, 77]. Wang *et al*. [76] conducted RNA-seq analysis of peripheral blood mononuclear cells (PBMCs) from patients with GPP before and after treatment. A significant enrichment in neutrophil function was found; given that neutrophils are commonly absent in PBMCs from healthy donors, the enrichment of neutrophil-specific genes in the dataset may have resulted from elevated proportions of low-density granulocytes (LDGs) in the PBMCs from patients with GPP. LDGs are a distinct subset of PBMCs, and have been reported to be present in many inflammatory diseases, such as systemic lupus erythematosus and psoriasis [94-96]. Differentially expressed genes (DEGs) were identified that were associated with nearly every aspect of neutrophil biology, including protein trafficking, granule formation, capture and rolling, and pattern recognition. After treatment, the severity of GPP diminished, and the expression of many important neutrophil-related genes was downregulated. Among them, formyl peptide receptor-like 1 (*FPRL1*) was noteworthy because it encodes a neutrophil G protein-coupled receptor and plays a pattern recognition role in chemotaxis [97]. Furthermore, FPRL1 is the receptor for LL37, illustrating the downstream portion of the mechanism discussed above [98].

One study also showed that the complement system is activated via the classic pathway in pustular psoriasis, and that the complement system further releases the neutrophil chemotactic fragment C5a, inducing pustular formation [99]. ■

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