Received: 14 January 2023 | Revised: 11 February 2023 | Accepted: 19 February 2023

DOI: 10.1111/exd.14776

RESEARCH ARTICLE

Experimental Dermatology WILEY

Clinical profile of patients with acute generalized pustular psoriasis with and without IL36RN mutations in multi-ethnic Johor Bahru, Malaysia

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Abstract

Generalized Pustular psoriasis (GPP), a rare and potentially life-threatening auto-inflammatory disease, is associated with *IL36RN* mutations. Here, we analyse the prevalence of *IL36RN* mutations in our multi-ethnic GPP cohort and assess differences in the clinical profile of patients with (*IL36RN*-positive) and without (*IL36RN*-negative) mutations. *IL36RN* mutations were present in 17.7% of 137 GPP patients (29.7% of Chinese cases, 17.3% of Malay cases, but 0% of Indian patients). 92% of these individuals carried the c.115+6 T>C mutation. Male: female ratio was 1:2.3. Females predominate in both groups with no significant difference between *IL36RN*-positive and *IL36RN*-negative individuals. The overall mean age (±SD) at disease onset for GPP was 37.6±17.2 years, but disease onset was significantly earlier in *IL36RN*-positive vs *IL36RN*-negative cases (mean age:30.6±18.92 vs. 39.2±16.49 years, $p = 0.027$). *IL36RN*-positive patients were less likely to have associated plaque psoriasis (52.4% vs. 83.5%, p-value = 0.002). There was no difference in the common clinical and laboratory manifestations or triggers of GPP between *IL36RN*-positive and -negative patients, except for geographic tongue which was significantly more common in *IL36RN*-positive patients (41.7% vs. 11.9%, p-value = 0.002). Annual flare rate was significantly higher in *IL36RN*-positive compared to *IL36RN*-negative (mean±SD of 1.92±1.32 vs. 1.46±0.90, $p = 0.041$) cases. However, no significant difference in the rate of hospitalization and length of hospital stay was observed between the two groups. These observations demonstrate that *IL36RN* disease alleles occur with varying frequencies among Asian populations and are associated with a severe, early-onset clinical phenotype.

KEYWORDS
generalized pustular psoriasis, IL36RN mutations, Malaysia, psoriasis, pustular psoriasis

1 | INTRODUCTION

Pustular psoriasis may be localized or generalized. In localized pustular psoriasis, the lesions are confined to the hands and feet. The two clinical variants are palmoplantar pustulosis and acrodermatitis continua of Hallipeau. Generalized pustular psoriasis (GPP) comprises acute GPP of von Zumbusch and a less acute variant known as Annular Pustular Psoriasis.[1–3] Acute generalized pustular psoriasis of von Zumbusch is a rare but most severe and potentially life-threatening variant of psoriasis. It is an autoinflammatory disease characterized by recurrent sudden flares of widespread painful erythema studded with sterile pustules which may coalesce to form lakes of pus.[1–4] Systemic manifestations such as high fever and fatigue/malaise as well as laboratory abnormalities namely leucocytosis, elevated C-reactive protein (CRP) levels, hypocalcemia, hypoalbuminemia and abnormal liver function tests often accompany GPP flares.

Flares are a hallmark of GPP and may occur spontaneously or provoked by triggers, including withdrawal of systemic corticosteroids, infections, stress, pregnancy and menstruation.[1–4] GPP is a heterogeneous disease with a broad spectrum of disease severity and a highly variable clinical course. GPP exerts a considerable impact on patients' physical and mental health as well as their quality of life.[4,5] Accurate diagnosis and prompt treatment are necessary to prevent potentially life-threatening complications such as sepsis, and renal, hepatic, respiratory and cardiovascular failure.[1–3] Reported mortality rates ranged from 4% to 32%.[2,5,6]

Acute GPP is predominantly characterized by an abnormal innate immune response.[7] Interleukin-36 (IL-36) is the key driver of disease pathology. The central role of IL-36 signalling in the pathogenesis of GPP was demonstrated by the identification of mutations of the *IL36RN* gene almost simultaneously in 9 Tunisian families with familial GPP and 3 out of 5 unrelated patients with sporadic GPP in 2011.[8,9] *IL36RN* codes for Interleukin-36 receptor antagonist (IL36Ra) which modulates the pro-inflammatory activities of IL-36. The recessive loss of function mutation of *IL36RN* abolishes the antagonistic effect of IL36Ra, allowing uninhibited IL36 signalling. Patients with *IL36RN* mutations were reported to have more severe disease with earlier disease onset and more systemic inflammation.[10] In this study, we analyse the prevalence of *IL36RN* mutations in our multi-ethnic patients with acute GPP and assess differences in their genetic status by gender and ethnicity. Variations in the clinical features of patients with and without *IL36RN* mutations were also examined.

2 | METHODS

This study was done by reviewing data collected from patients with acute GPP of von Zumbusch during the genetic screening from 2012 to 2019 with a standardized clinical record form and reviewing their electronic medical records till 2020. Data collected included demographic characteristics (age, gender and ethnicity), personal and family history of psoriasis and GPP, clinical features of pustular flares, trigger factors, laboratory findings and genetic status. The *IL36RN* and *CARD14* genes were screened by Sanger sequencing, using previously described primers[10–12] to sequence all coding exons and intron/exon junctions. This study was registered in the National Medical Research Register (NMRR-20-3004-57 880) and ethical approval was granted by the Medical Ethics and Research Committee (MREC), Ministry of Health Malaysia.

2.1 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0.0.0 (IBM Corp, Armonk, NY). Descriptive data were presented as means (±SD) or median (±interquartile range) for continuous variables and proportion (percentages) for categorical variables. Pearson's Chi-square (χ^2) or Fisher's exact test were used, where appropriate, to investigate the association between two categorical variables. For univariable analysis involving the comparison of continuous data, independent samples t-test was used for normally distributed data while Mann–Whitney U test was used for skewed data. Statistical significance was set at $p < 0.05$.

3 | RESULTS

Among 137 patients screened for disease alleles between 2012 and 2019, 24 (17.7%) harboured *IL36RN* mutations and four had *CARD14* mutations (p.Asp176His substitution). No *AP1S3* changes were detected in 101 patients screened for this gene. While digenic inheritance has been documented in GPP, we found none of the examined individuals carried mutations in both *CARD14* and *IL36RN*. Patients with CARD14 mutations were excluded from further analysis. The demographic characteristics and genotypes of the 24 patients with *IL36RN* mutations are depicted in Table 1. Twenty-two patients (92%) carried the c.115 + 6 T > C mutation, with six harbouring an additional p.Pro76Leu changes on the same chromosome. Thirteen individuals (54%) carried *IL36RN* mutations on both chromosomes while the remaining 46% presented with mono-allelic changes.

Table 2 compares key demographics, disease characteristics and common comorbid conditions of GPP in *IL36RN*-positive vs *IL36RN*-negative patients. Table 3 lists common clinical and laboratory manifestations of acute GPP in each group. Among 133 GPP patients, 75 (56.4%) were Malay, 37 (27.8%) were Chinese, 19 (14.3%) were Indian and 2 (1.5%) were of other ethnicities. *IL36RN* mutations, detected in 17.3% and 29.7% of Malay and Chinese patients respectively, were not present in any of the 19 Indian patients (Tables 1 and 2). Male to female ratio was 1: 2.3. Females predominated in both groups with no significant difference between IL36RN-positive and IL36RN-negative individuals (Table 2). Within patients who had IL36RN mutations, although males demonstrated a higher proportion of homozygous mutations than females (Table 1), the difference was not statistically significant (71.4% among males vs. 43.8% among females, $p = 0.37$).

TABLE 1 Demographic characteristics and IL36RN variants in patients with acute generalized pustular psoriasis with IL36RN mutations in Johor, Malaysia ($n = 24$).

Patient No.	Sex	Ethnicity	Onset age of GPP	Onset type	Mutation status	IL36RN variants[a]
1	F	Malay	21	GPP	Heterozygous	c.115+6 T>C/p.Pro76Leu
2	F	Malay	36	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
3	M	Malay	49	PV	Heterozygous	c.115+6 T>C/p.Pro76Leu
4	M	Chinese	32	ACH	Homozygous	c.115+6 T>C/c.115+6 T>C/p.Pro76Leu
5	F	Malay	20	PV	Heterozygous	c.115+6 T>C/neg
6	M	Malay	8	PV	Compound heterogyzous[b]	c.115+6 T>C/p.Ser113Leu
7	F	Chinese	21	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
8	F	Malay	0.25	PV	Homozygous	c.115+6 T>C/c.115+6 T>C/p.Pro76Leu
9	F	Chinese	60	PV	Heterozygous	c.115+6 T>C/neg
10	F	Chinese	29	PV	Heterozygous	c.115+6 T>C/p.Pro76Leu
11	F	Malay	42	GPP	Heterozygous	c.115+6 T>C/neg
12	M	Chinese	2	ACH	Homozygous	c.115+6 T>C/c.115+6 T>C
13	F	Malay	22	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
14	F	Malay	48	GPP	Heterozygous	c.115+6 T>C/neg
15	F	Chinese	7	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
16	F	Chinese	31	GPP	Heterozygous	c.115+6 T>C/neg
17	M	Chinese	6	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C/p.Pro76Leu
18	M	Chinese	45	PV	Homozygous	c.115+6 T>C/c.115+6 T>C
19	F	Chinese	55	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
20	F	Chinese	25	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
21	M	Malay	67	GPP	Heterozygous	c.115+6 T>C/neg
22	F	Malay	29	GPP	Heterozygous	p.Ser113Leu/neg
23	M	Malay	56	GPP	Homozygous	c.115+6 T>C/c.115+6 T>C
24	F	Malay	22	GPP	Heterozygous	c.115+6 T>C/–

[a]c.115+6 T>C and p.Pro76Leu are usually inherited on the same chromosome, from the same parent.

[b]The case with compound heterozygous mutation is excluded when comparing between homozygous and heterozygous mutations.

The mean age (±SD) at disease onset was 37.6±17.2 years across the entire cohort but was significantly earlier in *IL36RN*-positive compared to *IL36RN*-negative patients (mean age:30.6±18.92 vs. 39.2±16.49 years, $p = 0.027$). Age at GPP onset was also earlier in patients with homozygous than those with heterozygous mutations, but the difference was not statistically significant (mean 25.8±19.5 vs. 38.0±16.3 years, $p = 0.12$). The frequency of *IL36RN* mutations was higher in patients with paediatric-onset GPP (below 18 years old) than in those with adult-onset disease, but again, the difference was not statistically significant (29.4% vs 16.4%, $p = 0.19$). The most frequent comorbid conditions were hypertension (34.6%), dyslipidemia (31.6%), obesity (24.1%) and diabetes mellitus (16.5%), with no significant difference in prevalence between the two groups.

Sixty-five patients (48.9%) had preceding psoriasis vulgaris (PV) and two had preceding acrodermatitis continua of Hallipeau (ACH). Overall, 104 patients (78.2%) had associated PV including 37 patients who developed it post-GPP flare. Patients with *IL36RN* mutations were less likely to have associated PV (52.4% vs. 83.5%, p-value = 0.002). About 11.3% and 1.5% of patients reported a family history of PV and GPP respectively, with no significant difference between those with and without *IL36RN* mutations (Table 2). Disease triggers were reported by 117 (88%) GPP patients. The most common were stress (80.5%), followed by infection (48.9%), steroid exposure (30.8%) and pregnancy (26.9% of females) with no difference observed between *IL36RN*-positive and *IL36RN*-negative cases (Table 2). The mean (±SD) number of flares across the entire cohort was 1.54±1.00 per patient per year. However, the annual flare rate was significantly higher in IL36RN-positive compared to IL36RN-negative patients (1.92±1.32 vs. 1.46±0.90, $p = 0.041$).

There was no appreciable difference in the common clinical manifestations of acute GPP between the two groups, except for the finding of the geographic tongue (Table 3), which was more frequent in IL36RN-positive compared to IL36RN-negative individuals (41.7% vs. 11.9%, p-value = 0.002). Overall, common manifestations included systemic symptoms such as fever (63.2%) and malaise (48.9%), cutaneous symptoms such as pain (62.4%), pruritus (60.9%) and burning sensation (46.6%), as well as nail abnormalities (45.1%), lower limb oedema (34.6%) and arthritis (33.8%). Common

TABLE 2 Demographic and disease characteristics of acute GPP in patients with and without IL36RN mutations ($N = 133$).

Variables	All cases ($n = 133$)	No IL36RN ($n = 109$)	IL36RN ($n = 24$)	p-value[a]
Age of onset - GPP				
Mean (SD), years old	37.6 (17.20)	39.2 (16.49)	30.6 (18.92)	0.027[b]
GPP onset	*n* (%)	*n* (%)	*n* (%)	
Paediatric (<18 years)	17 (12.8)	12 (11.0)	5 (20.8)	0.191
Adult (18 years and above)	116 (87.2)	97 (89.0)	19 (79.2)	
Gender				
Male	40 (30.1)	32 (29.4)	8 (33.3)	0.701
Female	93 (69.9)	77 (70.6)	16 (66.7)	
Ethnicity				
Malay	75 (56.4)	62 (56.9)	13 (54.2)	0.018
Chinese	37 (27.8)	26 (23.9)	11 (45.8)	
Indian/Others	21 (15.8)	21 (19.3)	0 (0.0)	
Smoker				
No	125 (94.0)	102 (93.6)	23 (95.8)	1.000
Yes	8 (6.0)	7 (6.4)	1 (4.2)	
Drinker				
No	131 (98.5)	107 (98.2)	24 (100.0)	1.000
Yes	2 (1.5)	2 (1.8)	0 (0.0)	
Hypertension				
No	87 (65.4)	70 (64.2)	17 (70.8)	0.537
Yes	46 (34.6)	39 (35.8)	7 (29.2)	
Dyslipidemia				
No	91 (68.4)	73 (67.0)	18 (75.0)	0.444
Yes	42 (31.6)	36 (33.0)	6 (25.0)	
Obesity				
No	101 (75.9)	82 (75.2)	19 (79.2)	0.683
Yes	32 (24.1)	27 (24.8)	5 (20.8)	
Diabetes mellitus				
No	111 (83.5)	89 (81.7)	22 (91.7)	0.364
Yes	22 (16.5)	20 (18.3)	2 (8.3)	
Onset type				
GPP	66 (49.6)	51 (46.8)	15 (62.5)	NC[c]
PV	65 (48.9)	58 (53.2)	7 (29.2)	
ACH	2 (1.5)	0 (0.0)	2 (8.3)	
GPP with PV				
No	29 (21.8)	18 (16.5)	11 (45.8)	0.002
Yes	104 (78.2)	91 (83.5)	13 (54.2)	
Family history of psoriasis				
No	118 (88.7)	96 (88.1)	22 (91.7)	1.000
Yes	15 (11.3)	13 (11.9)	2 (8.3)	
Family history of GPP				
No	131 (98.5)	107 (98.2)	24 (100.0)	1.000
Yes	2 (1.5)	2 (1.8)	0 (0.0)	
Trigger Factor (TF)				
No	16 (12.0)	14 (12.8)	2 (8.3)	0.736
Yes	117 (88.0)	95 (87.2)	22 (91.7)	

TABLE 2 (Continued)

Variables	All cases ($n = 133$)	No IL36RN ($n = 109$)	IL36RN ($n = 24$)	p-value[a]
TF - Stress				
No	26 (19.5)	22 (20.2)	4 (16.7)	1.000
Yes	107 (80.5)	87 (79.8)	20 (83.3)	
TF - Steroid exposure				
No	92 (69.2)	74 (67.9)	18 (75.0)	0.495
Yes	41 (30.8)	35 (32.1)	6 (25.0)	
TF - Infection				
No	68 (51.1)	53 (48.6)	15 (62.5)	0.218
Any infection (including URTI)	65 (48.9)	56 (51.4)	9 (37.5)	
TF - Pregnancy ($n = 93$, females)				
No	68 (73.1)	59 (76.6)	9 (56.3)	0.122
Yes	25 (26.9)	18 (23.4)	7 (43.8)	
Number of flares per year, median (IQR)	1 (1)	1 (1)	1 (2)	0.064[d]

Abbreviations: ACH, Acrodermatitis continua of Hallopeau; GPP, generalized pustular psoriasis; IQR, interquartile range; NC, not computed; PV, psoriasis vulgaris; SD, standard deviation; TF, Trigger factor.

[a]Unless otherwise stated, Pearson's Chi-square (χ^2) or Fisher's exact test was used to compute p-values.

[b]Independent samples t-test was used for analysis.

[c]Mann-U Whitney test was used as the data was positively skewed.

[d]NC; not computed as the number of cases in ACH are too small.

laboratory abnormalities included elevated ESR (82.1%), elevated CRP (87.2%), leukocytosis (66.4%), hypoalbuminemia (28.7%), elevated ALT (13.4%) and elevated creatinine (6.3%). For all laboratory investigations analysed, there was no significant difference between patients with and without IL36RN mutations (Table 3).

Ninety-seven (72.9%) patients were admitted for acute GPP with no difference in hospitalization rate observed between those with and without mutations (75.0% vs.72.5%, $p = 0.80$). The overall length of hospital stay (LOS) was 11.2 ± 11.8 days with no difference observed between the 2 groups. The mean DLQI observed in 79 patients who underwent this assessment during a disease flare (14 *IL36RN*-positive and 65 *IL36RN*-negative individuals) was 13.3 ± 7.1 with no significant difference between those with and without mutations. Most patients had been treated with conventional systemic agents for their acute flares, namely acitretin (85 patients, 63.9%), methotrexate (37 patients, 27.8%) and cyclosporin (24 patients, 18%). Biologics used to treat GPP flares in 26 (19.5%) patients included spesolimab (5 patients), adalimumab, ustekinumab and secukinumab (4 patients each), etanercept (3 patients), infliximab, rizankizumab and guselkumab (2 patients each).

Acitretin, our drug of choice for GPP flares was effective in 92.9% of 85 patients, with a mean time to pustular clearance (available in 75 of patients) of 21.6 days (range 5 to 60 days). The baseline severity of most flares was either not available or not GPP-specific except for the 5 patients in a clinical trial for spesolimab, whereby GPPGA (Generalized Pustular psoriasis Physician Global Assessment) was measured. However, the body surface area involved in GPP flares was documented in at least one flare in 91% of patients ranging from 5% to 100%, but it was unclear whether this captured BSA with pustules or just erythema and scaling. Comparison of the effectiveness of various treatments in patients with and without IL36RN mutations was not feasible because of variation in assessing the severity of GPP flares due to the lack of a standard severity assessment tool and outcome measure. Seven patients had potentially life-threatening complications attributed to sepsis with one acute respiratory distress syndrome, one renal and one liver failure. Two patients succumbed to sepsis yielding a mortality rate of 2.2% among 133 GPP patients.

4 | DISCUSSION

IL36RN mutations account for 20% to 50% of GPP cases.[8–18] Here, we found *IL36RN* mutations in 29.7% and 17.3% of Chinese and Malay patients, respectively but in none of the 19 Indian cases that we examined. While IL36RN disease alleles have been described in various ethnic groups, with the highest prevalence observed among patients of European (34.7%) and East Asian (28.8%) descent,[12] there was only one study in which a homozygous *IL36RN* mutation was identified in two Pakistani siblings with GPP.[19] Thus, *IL36RN* disease alleles may be genuinely rarer in South Asia. However, further studies are needed to ascertain this.

All except one of our *IL36RN*-positive patients carried at least one copy of $115 + 6\ T > C$, the most common mutation in Asia.[11] The patient who carried a single copy of p.Ser113Leu, the predominant disease allele in Europeans, has a mixed descent from the Malay

TABLE 3 Common clinical and laboratory manifestations of acute GPP in patients with and without IL36RN mutations ($N = 133$).

Variables	All cases ($n = 133$)	No IL36RN ($n = 109$)	IL36RN ($n = 24$)	p-value[a]
Geographic tongue	*n* (%)	*n* (%)	*n* (%)	
No	110 (82.7)	96 (88.1)	14 (58.3)	0.002
Yes	23 (17.3)	13 (11.9)	10 (41.7)	
Uveitis				
No	129 (97.0)	106 (97.1)	23 (95.8)	0.553
Yes	4 (3.0)	3 (2.8)	1 (4.2)	
Nail Abnormalities				
No	73 (54.9)	62 (56.9)	11 (45.8)	0.325
Yes	60 (45.1)	47 (43.1)	13 (54.2)	
Arthritis				
No	88 (66.2)	71 (65.1)	17 (70.8)	0.593
Yes	45 (33.8)	38 (34.9)	7 (29.2)	
Lower limb oedema				
No	87 (65.4)	71 (65.1)	16 (66.7)	0.887
Yes	46 (34.6)	38 (34.9)	8 (33.3)	
Malaise (systemic)				
No	68 (51.1)	57 (52.3)	11 (45.8)	0.567
Yes	65 (48.9)	52 (47.7)	13 (54.2)	
Fever (systemic)				
No	49 (36.8)	44 (40.4)	5 (20.8)	0.073
Yes	84 (63.2)	65 (59.6)	19 (79.2)	
Pain (cutaneous)				
No	50 (37.6)	44 (40.4)	6 (25.0)	0.159
Yes	83 (62.4)	65 (59.6)	18 (75.0)	
Burning (cutaneous)				
No	71 (53.4)	61 (56.0)	10 (41.7)	0.204
Yes	62 (46.6)	48 (44.0)	14 (58.3)	
Pruritus (cutaneous)				
No	52 (39.1)	44 (40.4)	8 (33.3)	0.523
Yes	81 (60.9)	65 (59.6)	16 (66.7)	
Elevated ESR ($n = 106$ tested)				
No	19 (17.9)	14 (16.1)	5 (26.3)	0.326
Yes	87 (82.1)	73 (83.9)	14 (73.7)	
Elevated CRP ($n = 109$ tested)				
No	14 (12.8)	12 (13.3)	2 (10.5)	1.000
Yes	95 (87.2)	78 (86.7)	17 (89.5)	
Elevated ALT ($n = 127$ tested)				
No	110 (86.6)	91 (86.7)	19 (86.4)	1.000
Yes	17 (13.4)	14 (13.3)	3 (13.6)	
Elevated creatinine ($n = 127$ tested)				
No	119 (93.7)	98 (93.3)	21 (95.5)	1.000
Yes	8 (6.3)	7 (6.7)	1 (4.5)	
Hypoalbuminemia ($n = 122$ tested)				
No	87 (71.3)	71 (70.3)	16 (76.2)	0.587
Yes	35 (28.7)	30 (29.7)	5 (23.8)	

TABLE 3 (Continued)

Variables	All cases ($n = 133$)	No IL36RN ($n = 109$)	IL36RN ($n = 24$)	p-value[a]
Leucocytosis > 12 000 ($n = 131$ tested)				
No	44 (33.6)	36 (33.3)	8 (34.8)	0.894
Yes	87 (66.4)	72 (66.7)	15 (65.2)	
Elevated ASOT ($n = 88$ tested)				
No	59 (67.0)	50 (69.4)	9 (56.2)	0.310
Yes	29 (33.0)	22 (30.6)	7 (43.8)	
Hypocalcemia ($n = 63$ tested)				
No	61 (96.8)	48 (96.0)	13 (100.0)	1.000
Yes	2 (3.2)	2 (4.0)	0 (0.0)	
Fever AND leucocytosis ($n = 131$ tested)				
No	73 (55.7)	62 (57.4)	11 (47.8)	0.401
Yes	58 (44.3)	46 (42.6)	12 (52.2)	

Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
[a]Pearson's Chi-square (χ^2) or Fisher's exact test was used to compute p-values.

and Bajau indigenous tribes of Sabah, Malaysia, and was unaware of any European origin. The overall female preponderance observed, consistent with other studies,[5,6,12,17,20–23] could not be attributed to gender variation in the prevalence of *IL36RN* mutations in this cohort (females 17.2%, males 20.0%, $p = 0.701$). A female preponderance in both *IL36RN*-positive and *IL36RN*-negative patients was also reported in other studies and may be due to hormonal or environmental influences rather than genetic factors.[12,17] Comorbid conditions namely hypertension, dyslipidemia, obesity and diabetes mellitus are common in both groups.

A recent meta-analysis of 10 studies, including 683 cases of GPP (351 with and 332 without PV), showed that *IL36RN* mutations are significantly more frequent in patients without PV (OR = 3.82, 95%CI 2.63–5.56).[24] The significantly higher prevalence of IL36RN mutations in our patients without PV confirmed this observation. The same meta-analysis also demonstrated a lower rate of IL36RN alleles in adult versus paediatric GPP (OR = 0.42, 95%CI 0.23–0.77). However, in our study, we did not find a significant difference in the frequency of IL36RN mutations between patients with paediatric- and adult-onset GPP, possibly due to the low number of cases.

Importantly, we found significant variation among the three major ethnic groups of Malaysia, highlighting the need to explore the ethnic variation of IL36RN mutations in the highly heterogenous population in Asia for future targeted therapy. This is particularly relevant with the recent approval of an interleukin-36 receptor inhibitor, spesolimab, for the treatment of GPP flares. Rapid pustular and skin clearance within 1 week after a single dose of IV spesolimab was demonstrated in Effisayil 1 study, the pivotal trial, which led to the approval of this first-in-class targeted therapy for GPP.[25]

We did not find any significant difference in the common clinical manifestations of GPP between patients with and without *IL36RN* mutations except for the predominance of geographic tongue in *IL36RN*-positive patients. Recent studies from Vietnam and China also showed a significantly higher prevalence of geographic tongue (GT) in patients who carried the c.115+6 T>C allele.[17,26] Unlike other studies[10,16,17] which showed that *IL36RN* mutations predict a higher risk of systemic inflammation, defined as fever >38°C and leucocytosis $>12\times10^8$/L, we found no difference in the rate of fever, leucocytosis in the two patient groups. As previously described in the literature,[10-12,16,17] we also found that the age of disease onset was significantly lower in patients with than those without *IL36RN* mutations (mean age:30.6 vs. 39.2 years, $p = 0.027$). However, we are not able to confirm the reported dosage effect of *IL36RN* on disease onset. Although the mean age of GPP onset was earlier in patients with homozygous than those with heterozygous mutations, the difference was not statistically significant (mean 25.8 vs. 38.0 years, $p = 0.119$). In our cohort, patients with *IL36RN* mutations had significantly more pustular flares per year but there was no difference in the rate of hospitalization and the length of hospital stay. The majority of GPP flares are triggered and common triggers are stress, infections and the use of systemic corticosteroids with no difference between the 2 sub-groups.

There are strengths and limitations to our study. To the best of our knowledge, this is the first study to show variation in the frequency of *IL36RN* mutations among the three major ethnic groups namely Malays, Chinese and Indians (South Asians) in Asia. GPP is a potentially life-threatening disease, and all our patients were managed by experienced dermatologists in a tertiary hospital, allowing us to confidently compare the clinical characteristics of GPP in patients with and without *IL36RN* mutations. However, the need for a standard disease severity assessment tool and outcome measure, variation in the severity of flares and its self-limiting nature preclude meaningful comparison of the effectiveness of standard of care treatment. The small number of patients although sizable for a rare disease in a single centre, may contribute to the lack of statistical significance found when comparing the variables of interest in this study.

5 | CONCLUSIONS

We found *IL36RN* mutations in about 17.7% of our Malaysian patients. We observed ethnic variation, highlighting the need for more studies to illuminate the genetic background of Asians with GPP. We validate previous studies which showed that *IL36RN* mutations predict early disease onset and absence of PV. Finally, we show that the prevalence of geographic tongue and flare frequency is significantly higher in patients with *IL36RN* mutations.

AUTHOR CONTRIBUTIONS

Study concept and design: SE Choon and F Capon. Acquisition, analysis, or interpretation of data: SE Choon, F Capon, PSK Tok, KW Wong, YT Lim, NM Nanu and JN Barker. Drafting of the manuscript: SE Choon, PSK Tok. Critical revision of the manuscript for important intellectual content: All authors.

ACKNOWLEDGEMENT

None. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

SEC declared paid activities as advisor, speaker or consultant for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Leo, Pharma, MSD, Novartis, Pfizer, Sanofi and UCB. Capon FC received grants and consultancy fees from Boehringer Ingelheim. JB received consultancy fees and grants from AbbVie, Almirall, Amgen, AnaptysBio, Boehringer Ingelheim, Bristol Meyers-Squibb, Celgene, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Samsung, Sienna, Sun Pharma and UCB. The other authors had no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Electronic health records are, by definition, considered "sensitive" data and cannot be shared via public deposition because of information governance restrictions to protect patient confidentiality. Access to study data is available on request from SE Choon, choonse@yahoo.co.uk.

IRB APPROVAL STATUS

This study was registered in the National Medical Research Register (NMRR-20-3004-57880) and ethical approval was granted by the Medical Ethics and Research Committee (MREC), Ministry of Health Malaysia.

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How to cite this article: Choon SE, Tok PSK, Wong KW, et al. Clinical profile of patients with acute generalized pustular psoriasis with and without IL36RN mutations in multi-ethnic Johor Bahru, Malaysia. *Exp Dermatol*. 2023;32:1263-1271. doi:10.1111/exd.14776