Original Article

Correlation of *IL36RN* and *CARD14* mutations with clinical manifestations and laboratory findings in patients with generalised pustular psoriasis

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Abstract

Background: Generalized pustular psoriasis (GPP) is a chronic disease associated with genetic factors related to mutations of the interleukin 36 receptor antagonist gene (*IL36RN*) and the caspase recruitment domain 14 gene (*CARD14*). However, the relevance of these mutations to the clinical features and severity of GPP remains unclear.

Aims: Our objective was to correlate the presence of *IL36RN* and *CARD14* mutations with the clinical and laboratory findings in patients with GPP.

Methods: This cross-sectional descriptive study was conducted in 64 subjects with GPP. Clinical manifestations were recorded and the severity was graded as mild, moderate, or severe. Routine laboratory tests were performed and blood samples were collected for Sanger sequencing. The clinical data of patients were compared among the different mutation groups.

Results: The two main variants of *IL36RN* were c.115+6T > C (p.Arg10ArgfsX1) and c.227C > T (p.Pro76Leu). The major *CARD14* mutations were c.2458C > T (p.Arg820Trp), c.1641C > T (p.Arg547Ser), and c.1753G > A transitions.

Provocative factors were uncommon in the group with both *IL36RN* and *CARD14* mutations. Drugs (unspecified), especially herbals, were the most common triggers. A history of psoriasis was frequent in patients with only *CARD14* mutations, but fever was uncommon. The c.1641C > T mutation was associated with leukocytosis > 15000/mm^3 and the c.1753G > A mutation was associated with hypoalbuminemia <3.8g/dL. Both the c.115+6T > C and c.227C > T variants of *IL36RN* were associated with fever ≥38.5°C while the c.115+6T > C variant was also associated with geographic tongue.

No gene mutations were associated with the total severity and severity grades.

Limitations: Four patients without the two major *IL36RN* mutations were excluded from the study.

Conclusion: The presence of *IL36RN* and *CARD14* mutations were associated with a history of psoriasis, various provocative factors, fever, leukocytosis, hypoalbuminemia, and geographic tongue. Further studies to explore the role of these mutations in therapeutic efficacy and disease outcomes are necessary.

Key words: Gene mutation, *IL36RN*, *CARD14*, generalized pustular psoriasis

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Plain Language Summary

Generalized pustular psoriasis (GPP) is a chronic disease associated with genetic factors related to *IL36RN* and *CARD14* mutations. This study was conducted to investigate the effects of *IL36RN* and *CARD14* mutations on the clinical appearance and laboratory findings in patients with GPP. Sixty-four patients with GPP participated in the study. Clinical manifestations and laboratory test results of the patients were recorded. Patients were graded according to the severity of GPP (mild, moderate or severe).

IL36RN and *CARD14* mutations were associated with a history of psoriasis, trigger factors and clinical features such as geographic tongue, fever, leukocytosis and hypoalbuminemia.

Introduction

Generalized pustular psoriasis (GPP) is a chronic, refractory skin disease. However, some patients present with an acute, life-threatening, rapidly progressive generalized pustular rash accompanied by fever, erythema, oedema, hypoalbuminemia and leukocytosis. Genetic factors lead to a dysregulated inflammatory response and play a fundamental role in the pathogenesis of this disease. The frequency of mutations in *IL36RN* and *CARD14* genes is significantly greater in patients with GPP than in healthy controls[1,2,4-7] and these mutations are involved in the pathogenesis of GPP[1-4]

The *IL36RN* gene on the long arm of chromosome 2 in region 2q14 encodes for the protein interleukin-36 receptor antagonist (IL-36Ra).[8] Excessive activation of the inflammatory pathway in keratinocytes has been implicated in the pathogenesis of pustular psoriasis. IL-36Ra prevents IL-36 from binding to its receptor impeding the activation of the inflammatory pathway in keratinocytes.

The *CARD14* gene encode component 14 of the caspase recruitment domain family, which is a class of molecules that bind to proteins that regulate apoptosis or initiation of the nuclear factor-kappa B pathway. *CARD14* mutations increase the caspase recruitment domain protein activity inducing keratinocyte activation of the nuclear factor-kappa B pathway and increased transcription of Interleukin 36 gamma; this leads to the development of inflammatory skin diseases, including pustular psoriasis. *CARD14* mutations may be responsible for pustular psoriasis independent of *IL36RN* mutations both in children and adults.[9,10]

The precise relationship between these gene mutations and the clinical manifestations of GPP remains unclear. Two *IL36RN* mutations (c.115+6T > C and c.227C > T) are associated with severe clinical forms of pustular psoriasis, such as generalized, early-onset, or progressive pustular psoriasis with severe systemic symptoms.[5,11–13] However, the relationship between *CARD14* mutations and severity of pustular psoriasis has not yet been investigated.

In this study we explore the relationship between *IL36RN* and *CARD14* mutations and the clinical characteristics of patients with GPP.

Material and Methods

Subjects

This cross-sectional descriptive study included 64 patients with GPP hospitalized for treatment at the Ho Chi Minh City Dermatology Hospital, South Vietnam and the Hanoi Central Institute of Dermatology, North Vietnam between October 2019 and October 2020. All recruited patients met the diagnostic criteria of the Japanese Dermatological Association.[14]

Ethical approval

All participants were provided with a detailed description of the study and signed a consent form. The study was approved by the Ethics Committee of the Institute of Clinical Research and Medicine in Hanoi, Vietnam (approval number: 6302/HDDD) and complied with the principles of the Declaration of Helsinki.

Study design

Data collection

Clinical data collected for all patients included age, sex, age of onset, personal and family history of psoriasis and GPP, precipitating factors, medication history and clinical symptoms and clinical features. Skin lesions were photographed for later comparison. Peripheral blood samples were collected for routine tests (total blood cell analysis, blood glucose, liver, and renal function, electrolytes, urinalysis), for monitoring parameters (white blood cell count, C-reactive protein and serum albumin concentration) and for sequencing.

Severity grading was performed in accordance with the Japanese Dermatological Association criteria.[14] Severity of erythema, pustulosis and oedema were scored from 0 to 3 and white blood cell count, C-reactive protein, serum albumin, and body temperature were scored from 0 to 2. The final score of each patient determined the grading as mild (score 0–6), moderate (score 7–10), or severe (score 11–17).[14]

Mutation analysis

Peripheral blood (2 mL) was collected in test tubes containing 1.5 mg/mL EDTA and sent to the Centre for Molecular Biomedicine, University of Medicine and Pharmacy, Ho Chi Minh City for sequencing. DNA was extracted using a GeneJET Genomic DNA purification kit (Thermo Scientific,

Waltham, MA, USA) and stored at −30°C. DNA samples were quantified for purity and concentration using a nanodrop (Thermo Scientific).

Primers for PCR and sequencing of exons and flanking introns were designed using the CLC Main Workbench v.5.5(Quiagen, USA). The National Center for Biotechnology Information Consensus CDS (https://www.ncbi.nlm.nih.gov/projects/CCDS/CcdsBrowse.cgi) was used to obtain information regarding the attributed genomic and coding structures of *CARD14* (NG_032778.1 and NM_024110.4) and *IL36RN* (NG_031864.1 and NM_012275.3). The PCR process was conducted in 25-µL reactions containing 1X PCR buffer, 0.1 µM of forward and reverse primers each, 25–50 ng genomic DNA, and other essential chemicals. The temperature was set based on the phase of the process.

PCR reaction products were checked by electrophoresis (30 min at 100 V) on 1.5% agarose gel with 0.5X Tris- Borate-EDTA buffer. Samples were analyzed with a 1 kb plus DNA scale for size comparison. The products were clarified with the ExoSAP-IT reagent (Thermo Scientific). BigDye™ Terminator v3.1 Cycle Sequencing Kit was used for sequencing. The nucleotide sequence of the gene was determined by the automatic sequencing machine ABI 3500 Genetic Analyzer (Applied Biosystems). The CLC Main Workbench v5.5 software was used to align the target gene sequences in the samples and the mitochondrial DNA sequences on the National Center for Biotechnology Information to detect mutations in the gene, and the PolyPhen-2 software was used to predict the potential pathogenicity of the variations.

Statistical methods

Data were analyzed using the SPSS 20.0 software (version 20.0; SPSS Inc., Chicago, IL, USA). The results were presented as mean (standard deviation), median (range) or proportion. For normally distributed data, comparisons between groups were performed by the independent sample *t*-test or the one-way analysis of variance. For skewed data, we applied the Mann–Whitney *U* rank-sum test while for numeric data the Pearson's χ^2 test or the Fisher's exact test was used. A $P < 0.05$ was considered significant.

Results

Mutation analysis

There were 28 (43.8%) patients with *CARD14* mutations alone and 10 (15.6%) with *IL36RN* mutations alone. Mutations in both *CARD14* and *IL36RN* were present in 22 (34.4%) patients. The remaining 4 (6.3%) patients had no mutations in either gene and they were excluded from subsequent analysis.

IL36RN mutations

The two main variants of *IL36RN* identified on sequencing were c.115+6T > C and c.227C > T. Homozygous c.115+6T > C was the most prevalent type, present in 21 (32.8%) patients. Both heterozygous and homozygous c.115+6T > C variants together accounted for 29 (45.3%) of the mutations observed while heterozygous and homozygous c.227C > T variants were present in 11 (17.2%) patients.

A novel heterozygous c.96T > G (p.His32Gln) variation was found in exon 3 in 2 (3.1%) cases. Using the PolyPhen-2 software this variant had a score of 0.00 and was predicted to be benign. Two heterozygous variants (c.304C > T and c.386A > G) were detected in exon 5 in 1 patient each. The PolyPhen-2 score of 0.473 for c.304C > T and 0.962 for c.386A > G indicated that these variants were potentially pathogenic.

None of these mutations were noted in the control group. The two variants c.115+6T > C and c.227C > T represented the majority of *IL36RN* mutations, while other detected mutations formed a very small proportion; thus, we only considered these two mutations for subsequent analysis.

CARD14 mutations

The c.2458C > T (p.Arg820Trp) transition was detected in 41 (64.1%) of the 64 patients with GPP. Other *CARD14* mutations included c.1641C > T (p.Arg547Ser) in 25 (39.1%) patients and c.1753G > A in 18 (28.2%) patients.

Two new mutations in exon 16 and exon 18 were also noted in one case each. These were heterozygous c.1717G > A (p.Ala573Thr and c.2113G > A (p.Val705Ile) mutations with Polyphen-2 scores of 0.911and 0.983 respectively which indicated potential pathogenicity.

Only the three most frequent *CARD14* mutations (c.2458C > T, c.1641C > T and c.1753G > A) were included in subsequent analyses.

Epidemiology, history, and triggering factors

The 60 patients (after excluding 4 patients with uncommon mutations) were classified into three groups based on their genotype:

- Mutations in *IL36RN* only
- Mutations in *CARD14* only
- Mutations in both *IL36RN* and *CARD14.*

The sociodemographic profiles of the patients are shown in Table 1.

No significant differences were noted between the subgroups with regard to the age, sex, region or age of onset. A history of psoriasis was frequently seen in patients with *CARD14* mutations alone ($P = 0.016$). Provocative factors include: corticosteroids, herbal medicines, stress, pregnancy, infection and drugs. Provocative factors were less commonly noted in patients with both *IL36RN* and *CARD14* mutations ($P = 0.038$).

Drugs were the most common trigger (19 patients; 29.7%) and herbal medicines were involved in 13 (20.3%) of these

cases. Other triggers included stress (11 patients; 17.2%) and infections (9 patients; 14.1%).

Clinical manifestations [Table 2]

The common findings in descending order of frequency were skin pain, fever, chills, itching and mucosal involvement. Acropustulosis was present in 10% of patients.

Although no significant differences in the frequency of clinical symptoms in the subgroups, the incidence of fever was significantly higher in the group with *IL36RN* mutations alone as compared with the group with *CARD14* mutations alone (χ^2 test, $P = 0.027$) [Table 3]. The c.115+6T > C gene variant was associated with geographic tongue ($P = 0.033$, odds ratio = 3.15) [Table 3].

Assessment of disease severity

The various clinical and laboratory parameters for disease severity are summarized in Table 4. The severity scores for individual parameters, severity grades, total severity and severity classification did not differ between the groups. However, when the *IL36RN* variants were analyzed separately, the c.115+6T > C and c.227C > T variants were found to be associated with fever (temperature ≥38.5°C) [Table 3].

The c.1641C > T mutation of *CARD14* was associated with leukocytosis >15000/mm^3 ($P = 0.038$, OR = 3.077, 95% CI: 1.043–9.078) and the c.1753G > A variant was associated with a hypoalbuminemia <3.8 g/dL ($P = 0.042$, OR = 0.257) [Table 3].

Table 1: Epidemiology, history and provocative factors of the gene mutation groups

Group	*IL36RN* (*n* = 10)	*CARD14* (*n* = 28)	*IL36RN + CARD14* (*n* = 22)	*P*-value
Age	43.9 ± 22.97	34.71 ± 17.65	35.82 ± 17.69	0.4*
Gender (male/female)	6/4	13/15	8/14	0.45**
Region (HCMC/Hanoi)	6/4	21/7	16/6	0.658**
Personal history				
PV (without/with)	7/3	8/20	14/8	0.016**
PsA (without/with)	10/ 0	23/5	19/3	0.361**
EP (without/with)	7/3	24/4	20/2	0.304**
Family history				
GPP (without/with)	10/0	25/3	22/0	0.165**
PV (without/with)	10/0	25/3	21/1	0.447**
Age of onset	32.36 ± 21.9	29.27 ± 15.91	25.31 ± 16.83	0.528*
Provocative factors (without/with)	3/7	10/18	15/7	0.038**
Unspecified drugs (without/with)	4/6	20/8	17/5	0.098**
Herbal medicine (without/with)	9/1	21/7	19/3	0.445**
Stress (without/with)	6/4	24/4	20/2	0.084**
Infection (without/with)	8/2	23/5	20/2	0.613**

PV: psoriasis vulgaris, GPP: generalized pustular psoriasis, EP: erythrodermic psoriasis, PsA: psoriatic arthritis, HCMC: Ho Chi Minh City, *Statistically analyzed by one-way ANOVA test, ** Statistically analyzed by Pearson's chi-square test

Table 2: Clinical features of the mutation groups

Clinical symptoms	*IL36RN* (*n* = 10)	*CARD14* (*n* = 28)	*IL36RN + CARD14* (*n* = 22)	*P*-value
Itching (without/with)	6/4	16/12	9/13	0.442**
Skin pain (without/with)	1/9	7/21	7/15	0.418**
Fever (without/with)	2/8	17/11	8/14	0.050**
Malaise (without/with)	6/4	20/8	17/5	0.603**
Chills (without/with)	3/7	13/15	11/11	0.561**
Arthralgia (without/with)	8/2	23/5	16/6	0.718**
Erythroderma (without/with)	7/3	21/7	19/3	0.49**
Nail involvement (without/with)	5/5	14/14	12/10	0.944**
Mucosal involvement (without/with)	5/5	14/14	12/10	0.944**
Geographic tongue (without/with)	5/5	21/7	13/9	0.278**
Palmoplantar pustulosis (without/with)	9/1	21/7	19/3	0.445**
Acropustulosis (without/with)	9/1	27/1	18/4	0.232**

* Statistically analyzed by one-way ANOVA test, ** Statistically analyzed by Pearson's chi-square test

Table 3: Association between gene variants and clinical manifestations

Clinical and laboratory findings	Mutation		*P*-value
Fever (≥37.5°C)	*IL36RN alone*[10]	*CARD14 alone*[28]	
No	2	17	0.027**
Yes	8	11	
Fever (°C)	c.115+6T > C (*IL36RN*)		
	Without[35]	With[29]	
<38.5	32	20	0.022**
≥38.5	3	9	
Geographic tongue	c.115+6T > C (*IL36RN)*		
	Without[35]	With[29]	
Without	27	15	0.033**
With	8	14	
Fever (°C)	c.227C > T *(IL36RN)*		
	Without[53]	With[11]	
<38.5	46	6	0.025**
≥38.5	7	5	
WBC (K/mm^3)	c.1641C > T *(CARD14)*		
	Without[39]	With[25]	
<15	30	13	0.038**
≥15	9	12	
Serum albumin (g/dL)	c.1753G > A *(CARD14)*		
	Without[45]	With[19]	
≥3.8	26	16	0.042**
<3.8	19	3	

WBC: white blood cell count, ** Statistically analysed by Pearson's chi-square test

Table 4: Clinical and laboratory characteristics, total severity score, and severity classification of the gene mutation groups

Evaluation of clinical symptoms (score)	*IL36RN* (*n* = 10)	*CARD14* (*n* = 28)	*IL36RN* + *CARD14* (*n* = 22)	*P*-value
Erythema (<3/≥3)	3/7	14/14	14/8	0.205**
Pustules (<3/≥3)	5/5	13/15	13/9	0.669**
Edema (<3/≥3)	6/4	13/15	13/9	0.604**
Fever (<2/≥2)	7/3	25/3	16/6	0.239**
Evaluation of laboratory findings				
WBC (K/mm^3) (<15/≥15)	7/3	18/10	14/8	0.935**
CRP (mg/dL) (<7/≥7)	2/8	11/17	9/13	0.484**
Serum albumin (g/dL) (≥3,8/<3,8)	5/5	21/7	15/7	0.345**
Total severity score	12.2 ± 2.34	11.14 ± 2.92	11 ± 3.2	0.546*
Severity classification (mild-moderate/severe)	3/7	10/18	9/13	0.83**

WBC: white blood cell count, CRP: C-reactive protein, * Statistically analyzed by one-way ANOVA test, ** Statistically analyzed by Pearson's chi-square test

Discussion

The role of *IL36RN* and *CARD14* mutations in pustular psoriasis has been studied exhaustively.[2] We detected *IL36RN* mutations in 32 of 64 (50%) patients with GPP, similar to the incidence (46.8%) in a report on 62 patients from China.[6] The c.115+6T > C variant was present in 29 (45.3%) of 64 patients and accounted for the majority of *IL36RN* mutations. This is similar to that reported from China (Zhu *et al*. 52.5%; Li *et al*. 38.7%)[13,15,16] but much higher than in studies from Japan (Farooq 14%; Sugiura 19.3%).[1,17]

Few studies have addressed the prevalence of *CARD14* mutations in pustular psoriasis.[3] *CARD14* mutations were noted in 50 (78.1%) of our 64 patients with GPP but were seen in only 21% in a study of 19 patients from Japan.[3] The two most common *CARD14* mutations observed were c.2458C >

T (41 patients; 64.1%) and c.1641C > T (25 patients; 39.1%). These two variants have earlier been observed in patients with psoriasis vulgaris.[9,18] The mutation c.526G > C (p.Asp176His) reported from Japan was not detected in our study.[4]

Drugs (unspecified) were frequent triggers of GPP (19 patients; 29.7%). Traditional medicines triggered the onset of GPP in 13 (20.3%) patients. Provocative factors played a significant role in triggering GPP in patients with *IL36RN* or *CARD14* mutations alone, but not in patients with both mutations together.

The issue of whether the age at onset of GPP is related to gene mutations remains controversial. Mutations in *IL36RN* were observed to be related to GPP occurrence early in life,[13,15] but Korber *et al.* did not note any relationship to age at onset.[5] We, too, did not observe any difference in the age at onset between the groups. It is likely that the age of onset is influenced by gene-environment interactions and immune responses rather than genetic factors alone.

Many studies have suggested that the mutant genotype is associated with the phenotypic expression of GPP.[11,12] In 233 patients with GPP, Hussain *et al.* found an association between the *IL36RN* mutations and severe clinical features (i.e., early onset, systemic inflammation).[12] Distinct *IL36RN* genotypes were appraised for the effect on phenotypic manifestations, such as diffuse or localized GPP. Null mutations were thought to be related to serious clinical symptoms because of completely loss of function of IL36Ra while hypomorphic mutations with partially altered the structure and function of IL36Ra could result in diverse clinical manifestations.[11]

We studied the role of different gene mutations in giving rise to the variation in forms and severity of GPP. The total severity score of patients with GPP did not differ between the three groups of gene mutations (*IL36RN, CARD14* and *IL36RN + CARD14).* Zhu *et al.* also found no difference in severity scores between groups with and without *IL36RN* mutations.[13] It is likely that GPP severity is not related to a single gene mutation or a combination of *IL36RN* and *CARD14* mutations, suggesting that additional factors influence severity. This is further supported by the occurrence of severe GPP in heterozygous variants [5] and the presence of homozygous variants with mild or no symptoms.[16] Gene modification, other mutated genes, interactions between gene mutations, polyallelic inheritance, and the impact of environmental factors have been proposed to explain these observations.[11,17]

The group with only *IL36RN* mutations had fever more frequently than the group with only *CARD14* mutations ($P = 0.027$). Both c.115+6T > C and c.227C > T variants were associated with high fever (≥38.5°C).

The c.115+6T > C variant was associated with geographic tongue in our patients, as has been previously observed by Liang *et al.*[19]

Leukocytosis and hypoalbuminemia are indicators of severity in patients with GPP.[14] Zhu *et al*. found *CARD14* mutations to be associated with leukocytosis and hypoalbuminemia but not *IL36RN* mutations.[13] We found the c.1641C > T to be associated with leukocytosis and the c.1753G > A with hypoalbuminemia. However, the most frequent *CARD14* mutation (c.2458C > T) was not significant correlated with either clinical symptoms or laboratory parameters.

Limitations

There were few GPP patients without both mutations and these patients were excluded from analysis.

Conclusion

Our study showed that mutations in *IL36RN* and *CARD14* are associated with triggering factors and some clinical features of GPP, such as fever ≥38.5°C, geographic tongue, leukocytosis and hypoalbuminemia.

There were statistical differences in some clinical and laboratory findings in GPP patients with and without gene mutations that could aid genetic diagnosis. The mechanism by which these gene mutations influence the progression of GPP is only partly understood. GPP should not be viewed as a single-gene disease, but as the combined result of genetic factors, immune responses and environmental influences. Larger studies to clarify the role of mutations in the varied clinical presentation of patients with GPP need to be planned. Future randomized controlled clinical studies may provide more data and to establish standard treatments for generalized pustular psoriasis based on the genetic profile.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Abbreviations:

IL36RN - Interleukin-36 receptor antagonist gene
IL-36Ra - Interleukin-36 receptor antagonist protein
CARD14 - caspase recruitment domain 14
GPP - generalized pustular psoriasis

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