

Effect of AMPK Subunit Alpha 2 Polymorphisms on Postherpetic Pain Susceptibility in Southwestern Han Chinese

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Introduction: Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) can influence energy metabolism. Energy metabolism imbalance is closely associated with the occurrence of neuropathic pain (NeP). Rs10789038 and rs2796498 are genetic polymorphisms of *PRKAA2*, the gene encoding AMPK, which is closely related to energy metabolism imbalance. This study aimed to explore the relationship between *PRKAA2* and postherpetic neuralgia (PHN) in the southwestern Chinese Han population.

Methods: This study enrolled 132 PHN patients and 118 healthy subjects. The rs10789038 and rs2796498 *PRKAA2* genotypes were identified in all participants. The association between these single nucleotide polymorphisms and PHN susceptibility was evaluated in the dominant and recessive models. Haplotype analysis of patients with PHN and healthy controls was performed.

Results: The PHN patients were older than the healthy subjects ($P < 0.05$); however, the other clinical characteristics between two groups were not significantly different (all $P > 0.05$). Genotypes and allele frequencies differed significantly between PHN patients and healthy subjects in the rs10789038 polymorphism ($P < 0.05$), but not in rs2796498 ($P > 0.05$). In addition, the GG haplotype of rs10789038-rs2796498 correlated negatively with PHN occurrence in haplotype analysis ($P < 0.05$).

Conclusion: PHN occurrence may be related to the *PRKAA2* rs10789038 A>G genetic polymorphism in the southwestern Chinese Han population.

Keywords: AMPK, *PRKAA2*, polymorphism, postherpetic neuralgia

Introduction

Herpes zoster is a viral skin disease that often causes severe pain.¹ Postherpetic neuralgia (PHN) is defined as persistent or recurrent neuropathic pain (NeP) for more than three months after clinical healing of the rash.² PHN incidence in patients with herpes zoster is approximately 5 to 30% and approximately 30–50% in patients with a course of more than one year.³ The daily life and mental state of patients are affected in severe cases.⁴ PHN is a typical form of NeP.⁵ NeP is clinically characterized by hyperalgesia, allodynia, and dysesthesia.⁶ Studies on NeP pathogenesis^{7–10} and treatment^{11,12} have made a lot of breakthrough progress. However, few studies have described the pathogenesis of PHN. Therefore, more studies on PHN pathogenesis and intervention measures are needed urgently.

Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) is an important protein that regulates cell energy homeostasis, as well as a hotspot in translational medicine research.¹³ In mammalian cells, AMPK may be involved in the regulation of cell energy balance.¹⁴ Our previous study found that abnormal energy metabolism in rat spinal cord astrocytes is closely related to NeP, and that AMPK plays an important role in abnormal cellular capacity metabolism.¹⁴ In our recent study, we also found that dexmedetomidine could alleviate NeP by activating AMPK in a mouse model of chronic constriction injury.¹⁵ AMPK consists of three subunits - α , β , and γ , the first of which is the functional unit.¹⁶ AMPK α has two subtypes, $\alpha 1$

and $\alpha 2$, encoded by the *PRKAA1* and *PRKAA2* genes, respectively.^{17–19} Studies have shown that drug transporter gene polymorphisms can affect the activity of their protein products and lead to abnormal drug metabolism.^{20,21} Therefore, AMPK gene polymorphisms may also affect AMPK activity and lead to disease. The current literature on *PRKAA2* and diseases mainly includes diabetes-related studies.^{22,23} Other studies on AMPK polymorphisms have mainly focused on cancer and polycystic ovary syndrome,^{24–26} and no studies related to PHN have been reported. Thus, the purpose of this study was to investigate the relationship between *PRKAA2* and PHN in the southwestern Chinese Han population.

Materials and Methods

Patients

This study included 132 PHN patients and 118 healthy subjects from the Chongqing Hospital of Traditional Chinese Medicine. The inclusion criteria were: PHN (persistent or recurrent pain for more than three months after clinical healing of the rash)² and pain with a numerical rating scale ≥ 4 . Patients with hepatic, renal, neuromuscular, or nerve system diseases were excluded from the study.

The clinical characteristics of PHN patients and healthy subjects are collected, including sex, age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose. The research proposal was approved by the Ethics Committee of Chongqing Hospital of Traditional Chinese Medicine (2021-ky-67), and the study was conducted according to the Declaration of Helsinki principles. All subjects signed written consent forms. All subjects included in the experiment were of Han Chinese ethnicity.

DNA Extraction and Genotyping

Genomic DNA was isolated from peripheral venous blood using an SQ blood DNA kit (Cat. No. D5032-01, Omega, Norcross, Georgia, USA) according to the manufacturer's protocol and stored at 4 °C (long-term storage at –80 °C). The rs10789038 and rs2796498 polymorphisms of *PRKAA2* were used for genotyping. The primers used for the polymerase chain reaction (PCR) are listed in Table 1. The PCR reaction system consisted of 25 μ L with less than 20 ng of DNA template, 0.4 μ mol·L^{–1} of primer, and 12.5 μ L PCR Mix [2X T5 Super PCR Mix (Basic), Cat. No. TSE008, Tsingke Biotechnology, Chongqing, China]. The PCR reaction procedure was set according to the reference conditions of the kit, and the experiment was carried out after optimizing our preliminary experiment. The PCR products were sequenced by Tsingke Biotechnology Co. Ltd (Chongqing, China). The correlation between the rs10789038 and rs2796498 polymorphisms of *PRKAA2* and PHN was analyzed according to the gene sequencing results.

Table 1 PCR Primer Sequences of rs10789038 and rs2796498 Polymorphisms

Primers	Primer Sequences (5' to 3')
rs10789038-F	5'-GGGCCTTGTTTCTTCCCT-3'
rs10789038-R	5'-TGAACTCAGAACATACTAGGCA-3'
rs2796498-F	5'-GGCAGAGGTGAATTGTCAGT-3'
rs2796498-R	5'-CCTGACAGTCCAAGGCTACAC-3'

Statistics

The Hardy–Weinberg equilibrium of rs10789038 and rs2796498 was determined using the Nielsen method.²⁷ Genotypes and allele frequencies were compared between PHN patients and healthy subjects using the Chi-square test. Clinical data from PHN patients and healthy subjects were compared using the independent sample *t*-test. The correlation between each single nucleotide polymorphism (SNP) and PHN susceptibility was analyzed via binary logistic regression adjusted for age, sex, and BMI. The dominant and recessive models, as well as the homozygote and heterozygote comparisons were also assessed using

binary logistic regression. Linkage disequilibrium and haplotypes were assessed as previously described.²⁸ SPSS 26.0 (Chicago, Illinois, USA) was used to perform statistical analysis. Statistical significance was set at $P < 0.05$.

Results

Subject Characteristics

The clinical data of the PHN patients and healthy subjects are shown in Table 2. Overall, the PHN patients were older than the healthy subjects ($P < 0.05$); however, the other clinical data between the PHN patients and healthy subjects were not significantly different (all $P > 0.05$).

Association Study

The frequencies of the two SNPs are shown in Table 3. The rs10789038 and rs2796498 SNPs in PHN patients and healthy subjects conformed to the Hardy–Weinberg equilibrium ($P > 0.05$). This indicates that the population under investigation reached genetic equilibrium, showing that the data included in this study are credible. The genotype and allele frequencies of PHN patients and healthy subjects showed significant differences in rs10789038 ($P < 0.05$), but not in rs2796498 ($P > 0.05$).

Table 4 shows the different analysis models of the effect of *PRKAA2* gene polymorphisms on PHN. All statistical analyses were adjusted for sex, age, and BMI. Among all *PRKAA2* rs10789038 polymorphism genotypes, GG correlated negatively with AA; thus, subjects with the AA genotype might be at a higher risk of experiencing PHN [GG vs AA: ^aOR (95% CI) = 0.153 (0.032–0.731), ^aP = 0.019]. In the dominant model, the GG genotype would significantly decrease the risk of developing PHN, compared with the GG+AG genotype [AA+AG vs GG: ^aOR (95% CI) = 0.190 (0.039–0.927), ^aP = 0.040]. Compared with the AA genotype, AG+GG significantly decreased the risk of developing PHN in the recessive models [AA vs AG+GG: ^aOR (95% CI) = 0.547 (0.314–0.951), ^aP = 0.033]. Compared with the AA genotype of rs10789038, GG significantly decreased the risk of developing PHN [AA vs GG: ^aOR (95% CI) = 0.172 (0.035–0.842), ^aP = 0.030]. However, compared with the homozygous AA genotype of rs10789038, AG showed no statistical difference in PHN incidence [AA vs AG: ^aOR (95% CI) = 0.633 (0.354–1.133), ^aP = 0.124]. However, no significant correlation was seen between each genotype and the occurrence of PHN in all model analyses of the *PRKAA2* rs2796498 gene polymorphism ($P > 0.05$).

Table 2 The Demographic and Clinical Characteristics of PHN Patients and Healthy Subjects

Parameter	Healthy Controls (n=118)	PHN Patients (n=132)	P value
Gender			
Male	46	54	
Female	72	76	0.125
Age (years)	63.92±13.09	65.76±9.98	0.006
BMI (kg/m ²)	23.82±3.13	23.50±2.46	0.525
SBP (mmHg)	129±21	126±15	0.285
DBP (mmHg)	79±13	77±8	0.400
TG (mmol/L)	2.16±2.02	1.68±0.73	0.079
TC (mmol/L)	4.87±1.21	4.69±0.93	0.353
HDL-C (mmol/L)	1.21±0.28	1.22±0.37	0.785
LDL-C (mmol/L)	2.89±0.83	2.64±0.78	0.100
FBG (mmol/L)	7.15±2.40	7.20±2.72	0.917

Notes: Data are given as mean ± SD. Data were analyzed by independent sample *T* test. Significant results (p-value <0.05) were shown in bold type.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood-glucose.

Table 3 Comparisons of Allelic Frequencies of *PRKAA2* rs10789038 and rs2796498 Polymorphisms in PHN Patients and Healthy Subjects

Genotype	Healthy Controls (n=118)	PHN Patients (n=132)	P value
rs10789038			
AA	74 (62.7%)	100 (75.8%)	0.026
AG	36 (30.5%)	30 (22.7%)	
GG	8 (6.8%)	2 (1.5%)	
Alleles			
A	184(78.0%)	230(87.1%)	0.007
G	52(22.0%)	34(12.9%)	
HWE P	0.224	0.883	
rs2796498			
AA	18(15.3%)	14(10.6%)	0.345
AG	46(39.0%)	62(47.0%)	
GG	54(45.8%)	56(42.4%)	
Alleles			
A	82(34.7%)	90(34.1%)	0.925
G	154(65.3%)	174(65.9%)	
HWE P	0.127	0.603	

Notes: Data were analyzed by chi-square (χ^2) test. HWE, Hardy–Weinberg equilibrium. Significant results (p-value <0.05) were shown in bold type.

Table 4 The Association Between *PRKAA2* Genetic Polymorphisms and the Risk of PHN (Adjusted for Age, Gender and BMI)

SNPs	Comparisons	^a OR (95% CI)	^a P values
rs10789038	AA	1.000 (Reference)	
	AG	1.235 (0.651–2.344)	0.518
	GG	0.153(0.032–0.731)	0.019
	AA/AG vs GG (Dominant model)	0.190 (0.039–0.927)	0.040
	AA vs AG/GG (Recessive model)	0.547(0.314–0.951)	0.033
	AA vs GG (Homozygote comparison)	0.172(0.035–0.842)	0.030
	AA vs AG (Heterozygote comparison)	0.633(0.354–1.133)	0.124
rs2796498	AA	1.000 (Reference)	
	AG	1.765(0.790–3.941)	0.166
	GG	1.331(0.599–2.955)	0.483
	AA/AG vs GG (Dominant model)	0.863 (0.519–1.437)	0.572
	AA vs GG/AG (Recessive model)	1.527 (0.720–3.240)	0.270
	AA vs GG (Homozygote comparison)	1.329 (0.601–2.939)	0.483
	AA vs AG. (Heterozygote comparison)	1.766 (0.766–4.072)	0.182

Notes: Data were analyzed via binary logistic regression. ^aOR, odds ratio (adjusted for age, gender and BMI); 95% CI, 95% confidence interval. ^aP adjusted for age, gender and BMI. Significant results (p-value <0.05) were shown in bold type.

Haplotype Analysis

The results showed no linkage disequilibrium between *PRKAA2* rs10789038 and rs2796498. The D' value was 0.783, and the r^2 value was 0.243.

Haplotype analysis of PHN patients and healthy controls showed four haplotypes in the two SNPs, with significant differences between them ($P < 0.05$, Table 5). The GG haplotype was found only in healthy subjects, suggesting that it may reduce the risk of PHN ($P < 0.001$). There was no significant difference in the other three haplotypes between PHN patients and healthy subjects ($P > 0.05$).

Table 5 Haplotype Analysis of *PRKAA2* rs10789038 and rs2796498 with the Risk of PHN

	Case(Freq)	Control(Freq)	Odds Ratio [95% CI]	Pearson's p
A A	56.00(0.212)	41.95(0.178)	1.246 [0.798~1.945]	0.333333
A G	174.00(0.659)	142.05(0.602)	1.279 [0.888~1.840]	0.185755
G A	34.00(0.129)	40.05(0.170)	0.723 [0.441~1.186]	0.198194
G G	0.00(0.000)	11.95(0.051)	–	0.000217

Notes: Data were analyzed by online software, SHEsis.²⁸ Total control=236.0, total case=264.0, Global χ^2 is 2.030947 while $df=2$ (frequency<0.03 in both control and case has been dropped). Pearson's p value is 0.001048. Significant results (p-value <0.05) were shown in bold type.

Discussion

This is the first study to investigate the relationship between *AMPK α 2* gene polymorphisms and PHN in the southwestern Chinese Han population.

We hypothesized that *PRKAA2* gene polymorphisms may also cause changes in AMPK function, leading to unidentified changes in the body. A literature search revealed many studies on *PRKAA2* gene polymorphisms. A large part of the research has focused on the relationship between *PRKAA2* and diabetes mellitus and its related complications. For example, Li et al²² found that the rs10789038 and rs2796498 gene polymorphisms were related to the incidence of type 2 diabetes, and rs2796498 was associated with the occurrence of diabetic nephropathy. Keshavarz et al²⁹ reported that *PRKAA2* rs1418442 was slightly associated with the incidence of type 2 diabetes. Shen et al³⁰ reported that the *PRKAA2* rs2746342 polymorphism was significantly related to the occurrence of type 2 diabetes, while the rs2143754 polymorphism participates in fasting plasma glucose modulation. Horikoshi et al²³ found a *PRKAA2* gene polymorphism associated with insulin resistance and type 2 diabetes. In addition, studies have reported the association between *PRKAA2* gene polymorphisms and other diseases. Hoffman et al²⁵ demonstrated *PRKAA2* gene polymorphism involvement in non-Hodgkin lymphoma pathogenesis and progression. However, variants in *PRKAA2* genes were not associated with polycystic ovary syndrome.²⁴ Campa et al²⁶ found no statistically significant correlation between breast cancer risk and SNPs in *PRKAA2* genes in the European Prospective Investigation on Cancer.

In the present study, the correlation between the *PRKAA2* SNPs (rs10789038 and rs2796498) and PHN was investigated in the southwestern Chinese Han population. PHN patients were older than the healthy subjects. Although the healthy group was statistically significantly younger, the difference in age was only 1.8 years. Due to the small SD and large sample size, the mean was significantly different in the statistical test, but not large enough to assume that it influenced the makeup of the groups. Therefore, we believe that the difference was casual. In healthy subjects, the variation frequency of rs10789038 A>G in our study was 37.29%, which was similar to the 36.92% reported by Li et al.²² However, Li et al²² reported that the rs2796498 A>G gene variant frequency was 64.02%, which is different from the 84.75% that healthy subjects showed in this study. Gene-environment or gene-region interactions may be the reason for this difference. Our subjects were from southwest China (Chongqing City and surrounding provinces, including Guizhou, Sichuan, and Yunnan), while the participants of Li et al²² were from north China (Zhengzhou, Henan Province). In addition, the subjects in our study were from a specific ethnicity (Chinese Han population), while Li et al had a more diverse population. Therefore, the different genetic makeup (phenotype) may also affect studies. Li et al²² found that rs2796498 was closely related to diabetic nephropathy. However, we found no significant correlation between rs2796498 and PHN occurrence, which may be related to different gene frequencies. On the other hand, rs10789038 correlated significantly with PHN occurrence ($P < 0.001$). These results also indicate that the *PRKAA2* rs10789038 GG genotype may have reduced PHN incidence, whereas rs2796498 did not show this correlation (adjusted for sex, age, and BMI).

Haplotype analysis enables the combined detection of interacting susceptibility alleles on complex traits and the effects of linkage disequilibrium variants with specific haplotypes.^{31,32} This approach is more effective than analyzing SNPs alone. In the present study, haplotype analysis of PHN patients and healthy controls showed four haplotypes in the

two SNPs, and significant differences were found between the four haplotypes ($P < 0.05$). The GG haploid type was found only in healthy subjects, suggesting that it may reduce the risk of PHN ($P < 0.001$).

There are several strengths of this study. This study was the first to investigate the relationship between *PRKAA2* and PHN in the Chinese Han population. In addition, we show the first evidence that the rs10789038 polymorphism is significantly associated with susceptibility to PHN.

However, this study also has some limitations. The sample size was relatively small, and we selected only two SNPs to conduct genotype analysis, which cannot represent all *PRKAA2* gene polymorphisms. Second, the participants in this study were of southwestern Chinese Han ethnicity, a genetically homogenous group; therefore, this study may provide basis for further studies that evaluate the hypothesis tested here in other populations in China or in other ethnicities. Further research with larger sample sizes, more ethnic populations, and more polymorphic loci is required.

Conclusion

The present results indicate that *PRKAA2* rs10789038 had a significant effect on PHN susceptibility, while rs2796498 did not affect southwestern Han Chinese patients. However, multi-locus, multi-ethnic, and large-sample studies are needed to evaluate the role of *PRKAA2* polymorphisms in PHN.

Abbreviations

AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; NeP, neuropathic pain; PHN, Postherpetic neuralgia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood-glucose; PCR, polymerase chain reaction; OR, odds ratio; 95% CI, 95% confidence interval.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics Approval and Informed Consent

The research proposal was approved by the Ethics Committee of Chongqing Hospital of Traditional Chinese Medicine (2021-ky-67), and the study was conducted according to the Declaration of Helsinki principles. All subjects signed written consent forms.

Consent for Publication

Written consent was obtained from each of patients and healthy controls for all procedures and publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared no conflict of interest.

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