MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e924539
DOI: 10.12659/MSM.924539

Received: 2020.03.24
Accepted: 2020.04.17
Available online: 2020.05.19
Published: 2020.07.15

Association Between Ghrelin Gene Polymorphism and Cerebral Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE 1 Li Chen
BCF 1 Hua Zhao
DF 2 Jing Shen
ACG 3 Xiaoyu Ji

1 Department of Neurology, The Second Affiliated Hospital of Yangtze University and Jingzhou Central Hospital, Jingzhou, Hubei, P.R. China
2 Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Yangtze University and Jingzhou Central Hospital, Jingzhou, Hubei, P.R. China
3 Department of Neurology, The Affiliated Lianyungang Oriental Hospital of Xuzhou Medical University, Lianyungang, Jiangsu, P.R. China

Corresponding Author: Xiaoyu Ji, e-mail: jxy37@163.com
Source of support: Departmental sources

Background: The aim of this study was to explore the associations of ghrelin gene polymorphisms at rs26312, rs26802 and rs27647 with cerebral infarction.

Material/Methods: A total of 200 cerebral infarction patients in our hospital were enrolled as the disease group, while 200 healthy people were enrolled as the control group. Peripheral venous blood was collected from both groups, and the ghrelin gene polymorphisms at rs26312, rs26802, and rs27647 in nucleated cells were detected through sequencing.

Results: The genotype distribution at ghrelin gene *loci* rs26802 and rs27647 in the disease group was significantly different from that in the control group. The distribution of recessive model at ghrelin gene locus rs26802 in the disease group was different from that in the control group, in which the TG+GG frequency was evidently higher in the disease group. The AA genotype at ghrelin gene locus rs26312 was remarkably associated with the ghrelin gene expression level, and the expression level of ghrelin gene in the disease group was remarkably lower than that in the control group. The genotype at ghrelin gene locus rs26312 was associated with activated partial thromboplastin time (APTT), and APTT was significantly shorter in patients with GG genotype. The genotype at ghrelin gene locus rs26802 was associated with D-dimer, and the D-dimer level was significantly lower in patients with TG genotype. The genotype at ghrelin gene locus rs27647 was associated with prothrombin time (PT), and PT was obviously shorter in patients with TT genotype.

Conclusions: The ghrelin gene polymorphisms are remarkably associated with the occurrence of cerebral infarction.

MeSH Keywords: Association • Cerebral Infarction • Ghrelin

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/924539

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Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Cerebral infarction is one of the frequently-occurring diseases in middle-aged and elderly people around the world, and its morbidity rate is higher in China [1,2]. The occurrence of cerebral infarction is mainly related to the increase in blood viscosity and cerebral vascular stenosis, and it is also closely related to such factors as metabolism, vascular fragility, and age [3,4]. Cerebral infarction has a serious impact on the cerebral function of patients, causes ischemia and even necrosis in some brain tissues, and leads to function disorder or loss in some regions of the brain, thus greatly affecting the quality of life of patients after treatment, and can even be life-threatening. The pathogenesis of cerebral infarction is complex and may be related to the mutation and abnormal expression of multiple genes [5].

Gene polymorphism refers to the individual differences in alleles or genotypes at the same locus in the population, which increases or decreases susceptibility of the population to some diseases, or affects the gene expression, thereby affecting the occurrence of disease [6,7]. Studies have demonstrated that multiple gene polymorphisms affect the occurrence of cerebral infarction. For example, CTSS gene [8] and PPARG2 gene [9] polymorphisms are associated with the occurrence of cerebral infarction in the Chinese population, and the ALDH2 gene polymorphism affects the collateral circulation and prognosis of cerebral infarction patients [10]. As the ligand for the growth hormone secretagogue receptor, the ghrelin gene promotes the release of growth hormone, thereby affecting various biological functions. However, the association between ghrelin gene polymorphism and susceptibility to cerebral infarction has not been reported yet.

In this study, the ghrelin gene polymorphisms at loci rs26312, rs26802, and rs27647 in peripheral venous blood nucleated cells were studied in cerebral infarction patients and healthy people, combined with the haplotype analysis and detection of coagulation indexes, so as to explore the associations of ghrelin gene polymorphisms with cerebral infarction.

Material and Methods

General data

A total of 200 patients diagnosed with cerebral infarction in our hospital from 2017 to the present (disease group) and 200 healthy people at the physical examination center (control group) were enrolled in the study. The general and clinical data in both groups were collected, including name, admission ID, gender, age, body mass index (BMI), disease history, and drug allergy history. The mean age was (65.21±5.83) years old in the disease group and (64.92±4.24) years old in the control group. There were no statistically significant differences in such general data as age and gender between the 2 groups.

Inclusion criteria for cerebral infarction patients in disease group were: middle-aged and elderly patients with new-onset cerebral infarction, those with clinical symptoms of cerebral infarction such as headache, dizziness and epileptic seizure, those with cerebral ischemic lesions shown in brain CT and MRI, and those with cerebral vascular stenosis or occlusion and poor blood flow shown in cerebral angiography.

This study was approved by the Ethics Committee of Jingzhou Central Hospital. Signed written informed consent was obtained from all participants before the study began.

Sample collection and processing

About 6–8 mL of peripheral venous blood was collected from both groups and centrifuged using a centrifuge at 3000 rpm for 8 min within 2 h. Then, the upper-layer serum and mid-layer nucleated cells were transferred into new centrifuge tubes. The upper-layer serum was stored in liquid nitrogen for later detection, and the genomic deoxyribonucleic acid (DNA) was extracted from the mid-layer nucleated cells.

Genomic DNA extraction

The genomic DNA was extracted from the peripheral venous blood in both groups using the blood genome extraction kit (Tiangen, Beijing, China) in strict accordance with the instructions of the kit. According to the volume of sample, an appropriate amount of protease K solution was added into the centrifuge tube, and peripheral venous blood samples and buffer were also added. The mixture was mixed evenly using a vortex oscillator and incubated at 65°C for 8–10 min. Then, 2 mL of absolute alcohol was added into the samples, mixed evenly, and transferred into an absorption column. We added 2 mL of buffer into the absorption column, followed by centrifugation at 3000 rpm for 1 min. Finally, 200 μL of elution buffer was added into the absorption column, and the resulting solution was the genomic DNA.

Polymerase chain reaction (PCR) amplification and analysis of ghrelin gene polymorphisms at *loci* rs26312, rs26802, and rs27647

The polymorphic regions at ghrelin gene loci rs26312, rs26802, and rs27647 were amplified using the PCR instrument. The total PCR system was 25 μL, including 1 μL of forward primers, 1 μL of reverse primers, 0.5 μL of DNA template, 12.5 μL of high-fidelity heat-resistant Taq DNA polymerase, and 10 μL of dH_2O. The PCR conditions were: 95°C for 5 min, (95°C for

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Table 1. Allele distribution at ghrelin gene *loci* rs26312, rs26802, and rs27647.

Locus	Allele	Control group	Disease group	OR	95%CI	χ^2	*P*
rs26312	G	211 (0.527)	193 (0.482)	1.19	0.90–1.58	1.62	0.203
	A	189 (0.472)	207 (0.517)				
rs26802	T	213 (0.532)	178 (0.445)	1.42	1.07–1.87	6.12	0.013
	G	187 (0.468)	222 (0.555)				
rs27647	C	205 (0.512)	206 (0.515)	1.01	0.76–1.33	0.01	0.943
	T	195 (0.487)	194 (0.485)				

30 s, 57°C for 40 s, and 72°C for 35 s)×45 cycles, and 72°C for 5 min. The primers of polymorphic *loci* were:
Ghrelin gene locus rs26312:
forward (5'→3'): TGAGCAGGATGGAGAATTACAGG,
reverse (5'→3'): GTCCAAGTTCATCTTCTAGGCAC.
rs26802:
forward (5'→3'): TCTGCGGCATGTTCTGGATTT,
reverse (5'→3'): ATGTGTTGTCAGAGCCCTTTAG.
rs27647:
forward (5'→3'): GTGCTCCTTGTCAACAGCG,
reverse (5'→3'): GGGGAGTTTCAGGTTCCTGTA.
The PCR products were sent to Jiangsu Biotechnology Co. (Nanjing, China) for sequencing, and the polymorphisms at ghrelin gene *loci* were analyzed in both groups.

Detection of ghrelin gene expressions

The ghrelin gene expression was detected via reverse transcription-quantitative PCR (RT-qPCR) in both groups. The RNA sample was extracted using the TRIzol method and reversely transcribed into complementary deoxyribose nucleic acid (cDNA). The gene primers were designed using Primer Premier 5.0 and synthesized by Sangon (Shanghai, China):
Ghrelin:
forward (5'→3'): TACAAGAACCCGAAACTGACTCG,
reverse (5'→3'): ACATGAAGGTAGTCTCACTGCC.
The total PCR system was 25 μL, including 1 μL of forward primers, 1 μL of reverse primers, 0.5 μL of cDNA template, 12.5 μL of SYBR premix Taq, and 10 μL of dH_2O. The PCR conditions were: 94°C for 2 min, (95°C for 35 s, 56°C for 40 s, and 72°C for 35 s)×45 cycles, and 72°C for 5 min.

Detection of clinical indexes

The peripheral venous blood was extracted in both groups, and the clinical coagulation indexes prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer were detected within 2 h in the Clinical Examination Room of the Laboratory Department using the full-automatic coagulation analyzer.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 23.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Enumeration data were compared using the χ^2 test, and the Hardy-Weinberg equilibrium test was performed. Haplotype analysis was conducted using the SHEsis website. $P<0.05$ suggested the statistically significant difference.

Results

Allele distribution at ghrelin gene *loci* rs26312, rs26802, and rs27647

As shown in Table 1, the allele distribution at ghrelin gene locus rs26802 was different between the control group and disease group ($P=0.013$), and the T allele frequency in the disease group (178) was significantly lower than that in the control group (213).

Genotype distribution at ghrelin gene *loci* rs26312, rs26802, and rs27647

As shown in Table 2, the genotype distribution at ghrelin gene *loci* rs26802 ($P=0.026$) and rs27647 ($P=0.006$) in the disease group was significantly different from that in the control group. The TT genotype frequency at rs26802 in the disease group was obviously lower than that in the control group, while the CT genotype frequency at rs27647 in the disease group was obviously higher than that in the control group.

Analysis of polymorphisms at ghrelin gene *loci* rs26312, rs26802, and rs27647

As shown in Table 3, the distribution of recessive model at ghrelin gene locus rs26802 in the disease group was different from that in the control group ($P=0.033$), in which the TG+GG frequency was evidently higher in the disease group. The distribution of dominant model ($P=0.023$) and heterozygous model ($P=0.007$) at rs27647 in the disease group was also different

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Table 2. Genotype distribution at ghrelin gene *loci* rs26312, rs26802, and rs27647.

Locus	Allele	Control group		Disease group		OR	95%CI	χ^2	*P*
rs26312	GG	49	(0.245)	42	(0.210)	0.45	0.24–0.61	2.01	0.367
	GA	113	(0.565)	109	(0.545)				
	AA	38	(0.190)	49	(0.245)				
rs26802	TT	61	(0.305)	38	(0.190)	1.41	1.27–1.76	7.31	0.026
	TG	91	(0.455)	102	(0.510)				
	GG	48	(0.240)	60	(0.300)				
rs27647	CC	50	(0.250)	35	(0.175)	1.22	1.01–1.49	10.09	0.006
	CT	105	(0.525)	136	(0.680)				
	TT	45	(0.225)	29	(0.145)				

Table 3. Analysis of polymorphisms at ghrelin gene *loci* rs26312, rs26802, and rs27647.

	Locus	Genotype	Control group		Disease group		χ^2	P
Dominant model	rs26312	GG+GA	162	(0.810)	151	(0.755)	2.81	0.381
		AA	38	(0.190)	49	(0.245)		
	rs26802	TT+TG	152	(0.760)	140	(0.700)	1.51	0.583
		GG	48	(0.240)	60	(0.300)		
	rs27647	CC+CT	155	(0.775)	171	(0.855)	7.45	0.023
		TT	45	(0.225)	29	(0.145)		
Recessive model	rs26312	GG	49	(0.245)	42	(0.210)	2.14	0.401
		GA+AA	151	(0.755)	158	(0.790)		
	rs26802	TT	61	(0.305)	38	(0.190)	6.34	0.033
		TG+GG	139	(0.695)	162	(0.810)		
	rs27647	CC	50	(0.250)	35	(0.175)	2.34	0.451
		CT+TT	150	(0.750)	165	(0.825)		
Heterozygous model	rs26312	GG	49	(0.245)	42	(0.210)	1.93	0.485
		GA	113	(0.565)	109	(0.545)		
	rs26802	TT	61	(0.305)	38	(0.190)	3.95	0.058
		TG	91	(0.455)	102	(0.510)		
	rs27647	CC	50	(0.250)	35	(0.175)	8.34	0.007
		CT	105	(0.525)	136	(0.680)		
Homozygous model	rs26312	GG	49	(0.245)	42	(0.210)	2.74	0.331
		AA	38	(0.190)	49	(0.245)		
	rs26802	TT	61	(0.305)	38	(0.190)	2.38	0.351
		GG	48	(0.240)	60	(0.300)		
	rs27647	CC	50	(0.250)	35	(0.175)	3.01	0.134
		TT	45	(0.225)	29	(0.145)		

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Table 4. Haplotype analysis of ghrelin gene *loci* rs26312, rs26802, and rs27647.

Haplotype	Control group	Disease group	OR	95%CI	$\chi 2$	*P*
AGC	39.18 (0.098)	77.26 (0.193)	2.205	1.459–3.331	14.574	0.000
AGT	40.99 (0.102)	47.23 (0.118)	1.173	0.753–1.827	0.497	0.481
ATC	58.91 (0.147)	26.32 (0.066)	0.408	0.252–0.661	13.952	0.000
ATT	49.92 (0.125)	56.20 (0.140)	1.146	0.761–1.726	0.428	0.513
GGC	54.46 (0.136)	36.83 (0.092)	0.643	0.413–1.002	3.843	0.050
GGT	52.38 (0.131)	60.69 (0.152)	1.187	0.797–1.769	0.711	0.399
GTC	52.45 (0.131)	65.60 (0.164)	1.3	0.878–1.925	1.717	0.190
GTT	51.71 (0.129)	29.89 (0.075)	0.544	0.339–0.873	6.501	0.011

Table 5. Linkage disequilibrium analysis.

D’	rs26312	rs26802	rs27647
rs26312	–	0.631	0.033
rs26802	0.631	–	0.058
rs27647	0.033	0.058	–

from that in the control group, in which the CC+CT frequency in dominant model and CT frequency in heterozygous model were evidently higher in the disease group.

Haplotype analysis of ghrelin gene *loci* rs26312, rs26802, and rs27647

According to the haplotype analysis and linkage disequilibrium analysis of ghrelin gene *loci* rs26312, rs26802, and rs27647 (Tables 4, 5), the haplotype frequency of ghrelin AGC (*P*=0.000), ATC (*P*=0.000), and GTT (*P*=0.011) in the disease group was markedly different from that in the control group, in which the disease group had a markedly higher haplotype frequency of ghrelin AGC and a markedly lower haplotype frequency of ATC and GTT. Moreover, the linkage disequilibrium was higher at ghrelin gene *loci* rs26802 and rs26312 (D’=0.631).

Associations of genotypes at ghrelin gene *loci* rs26312, rs26802, and rs27647 with gene expressions

The detection results of the associations of genotypes at ghrelin gene *loci* rs26312, rs26802, and rs27647 with gene expressions revealed that the AA genotype at ghrelin gene locus rs26312 was remarkably associated with the ghrelin gene expression level (*P*<0.05), and the expression level of ghrelin gene in the disease group was remarkably lower than that in the control group (Figures 1–3).

Associations of genotypes at ghrelin gene *loci* rs26312, rs26802, and rs27647 with coagulation indexes

The genotype at ghrelin gene locus rs26312 was associated with APTT (*P*=0.031), and APTT was significantly shorter in patients with GG genotype. The genotype at ghrelin gene locus rs26802 was associated with D-dimer (*P*=0.043), and the D-dimer level significantly increased in patients with TG genotype. The genotype at ghrelin gene locus rs27647 was associated with PT (*P*=0.037), and PT was obviously shorter in patients with TT genotype (Table 6).

Discussion

The occurrence of cerebral infarction, one of the major diseases affecting the health of middle-aged and elderly people, is related to many factors [11,12]. The pathogenesis of cerebral infarction is mainly related to the metabolite level and vascular function in patients, and it is also affected by the expression of some genes or pathways [13]. Studies have shown that N-acetylcysteine plays an important role in the pathogenesis of cerebral infarction and can affect its prognosis [14], and substances such as acrolein are also involved in this process [15]. Therefore, studying the specific factors affecting the occurrence of cerebral infarction has importance in the prevention and treatment of disease.

The protein encoded by the ghrelin gene is the ligand for the growth hormone secretagogue receptor, which mainly regulates

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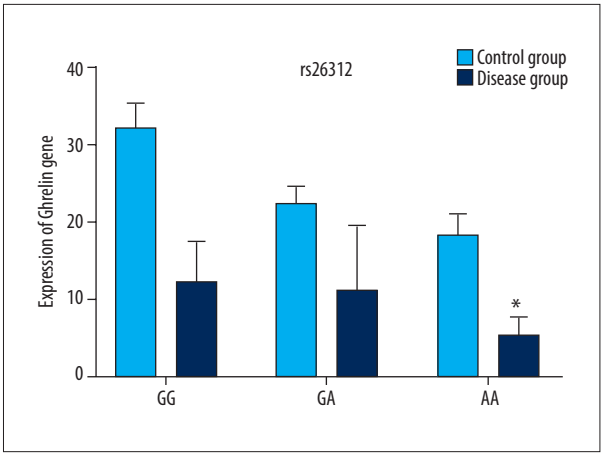

Figure 1. Association between genotype at ghrelin gene locus rs26312 and gene expression (* *P*<0.05 *vs.* other genotypes in control group or disease group).

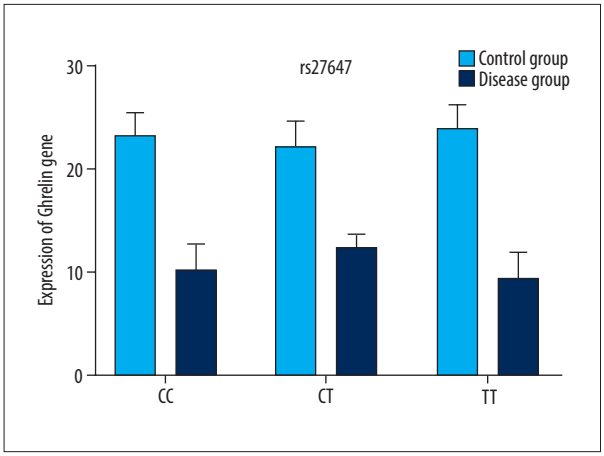

Figure 3. Association between genotype at ghrelin gene locus rs27647 and gene expression.

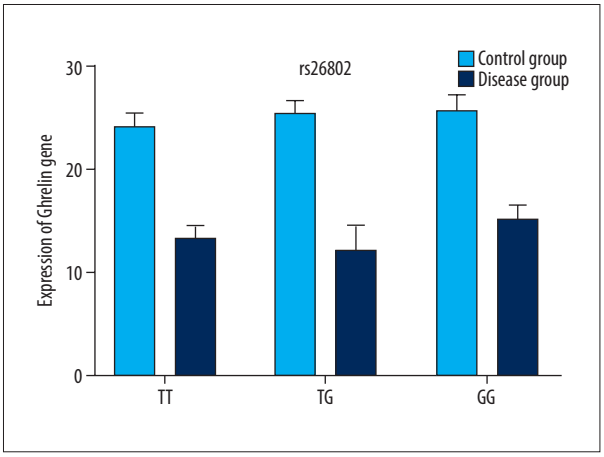

Figure 2. Association between genotype at ghrelin gene locus rs26802 and gene expression.

the concentration of growth hormone in the body and affects some of the body's functions through affecting the release of growth hormone, such as regulating growth and development, affecting sugar, lipid and protein metabolism, and relaxing the cardiovascular system [16,17]. It has been proved that the ghrelin gene polymorphisms can affect the occurrence and susceptibility to a variety of diseases, such as polycystic ovary syndrome [18], chronic hepatitis C [19], and type 2 diabetes mellitus [20]. In cerebral infarction patients, the effects of ghrelin gene polymorphisms have not been studied yet. In this study, it was found that the allele distribution at ghrelin gene locus rs26802 was different between the control group and disease group (*P*=0.013), and the T allele frequency in the disease group was significantly lower than that in the control group, indicating that the ghrelin gene polymorphisms can indeed affect the occurrence of cerebral infarction.

Table 6. Associations of genotypes at ghrelin gene *loci* rs26312, rs26802, and rs27647 with coagulation indexes.

Locus	Genotype	PT (s)			APTT (s)			D-dimer (mg/L)		
		Control group	Disease group	*P*	Control group	Disease group	*P*	Control group	Disease group	*P*
rs26312	GG	14	8	0.276	24	18	0.031	0.12	0.46	0.184
	GA	13	7		27	23		0.11	0.35	
	AA	15	9		28	22		0.23	0.38	
rs26802	TT	14	8	0.372	27	21	0.734	0.14	0.37	0.043
	TG	14	7		31	23		0.08	0.31	
	GG	15	8		28	22		0.15	0.51	
rs27647	CC	15	8	0.037	29	25	0.273	0.16	0.37	0.273
	CT	16	8		26	21		0.21	0.48	
	TT	12	6		32	23		0.18	0.42	

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The genotype distribution at ghrelin gene *loci* rs26802 (*P*=0.026) and rs27647 (*P*=0.006) in the disease group was significantly different from that in the control group. The TT genotype frequency at rs26802 in the disease group was obviously lower than that in the control group, while the CT genotype frequency at rs27647 in the disease group was obviously higher than that in the control group. The above results suggest that the genotypes at rs26802 and rs27647 can obviously affect the susceptibility of cerebral infarction patients. The population with rs27647 CT genotype has a significantly higher risk of cerebral infarction, while that with rs26802 TT genotype is less susceptible to cerebral infarction.

In this study, it was found through polymorphic analysis and modeling that the distribution of recessive model at ghrelin gene locus rs26802 in the disease group was different from that in the control group (*P*=0.033), in which the TG+GG frequency was evidently higher in the disease group. The distribution of dominant model (*P*=0.023) and heterozygous model (*P*=0.007) at rs27647 in the disease group was also different from that in the control group, in which the CC+CT frequency in dominant model and CT frequency in heterozygous model were evidently higher in the disease group, which demonstrate that the effects of ghrelin gene polymorphisms on cerebral infarction may be jointly realized by multiple genotypes at the same locus. According to haplotype analysis, the haplotype frequency of ghrelin AGC (*P*=0.000), ATC (*P*=0.000) and GTT (*P*=0.011) in the disease group was markedly different from that in the control group, in which the disease group had a markedly higher haplotype frequency of ghrelin AGC and a markedly lower haplotype frequency of ATC and GTT, suggesting that the combined analysis of 3 polymorphic *loci* of ghrelin may perform better in determining the susceptibility to cerebral infarction. The linkage disequilibrium was higher at ghrelin gene *loci* rs26802 and rs26312 (D'=0.631), confirming that the 2 *loci* jointly affect the ghrelin gene polymorphisms.

The AA genotype at ghrelin gene locus rs26312 was remarkably associated with the gene expression level (*P*<0.05), and the expression level of ghrelin gene in the disease group was remarkably lower than that in the control group, indicating that the effect of the ghrelin gene on cerebral infarction may occur through altering the expression level of the ghrelin gene and affecting the release of growth hormone.

We found that the genotype at ghrelin gene locus rs26312 was associated with APTT (*P*=0.031), and APTT was significantly shorter in patients with GG genotype. The genotype at ghrelin gene locus rs26802 was associated with D-dimer (*P*=0.043), and the D-dimer level was significantly higher in patients with TG genotype. The genotype at ghrelin gene locus rs27647 was associated with PT (*P*=0.037), and PT was obviously shorter in patients with TT genotype. These findings prove that the ghrelin gene polymorphisms can serve as an important predictive index for the clinical progression and prognosis of cerebral infarction.

Conclusions

These findings prove that the ghrelin gene polymorphisms can serve as an important predictive index for the clinical progression and prognosis of cerebral infarction.

Conflict of interest

None.

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