MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2021; 27: e933444
DOI: 10.12659/MSM.933444

Received: 2021.06.04
Accepted: 2021.07.29
Available online: 2021.08.24
Published: 2021.11.04

Association of Single-Nucleotide Polymorphisms of Gab1 Gene with Susceptibility to Meningioma in a Northern Chinese Han Population

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Financial support: This research was supported by the Beijing-Tianjin-Hebei Basic Research Cooperation Special Project (H2018206675)
Conflict of interest: None declared

Background: The Gab1 gene has an important role in cell proliferation in meningioma via various signaling pathways. However, the relationship between polymorphisms of the Gab1 gene and meningioma remains unknown. In this study, we aimed to investigate the plausible association of single-nucleotide polymorphisms (SNPs) of the Gab1 gene and meningioma risk in a northern Chinese Han population.

Material/Methods: This case-control study included 205 patients with meningioma and 297 healthy controls. Four loci of the Gab1 gene were genotyped using the multiplex snapshot technique. The odds ratio (OR) and 95% confidence interval (CI) were calculated by chi-squared and logistic regression analysis. The distributions of Gab1 SNP genotypes and allele frequencies were compared between patients with meningioma and healthy controls and among patients stratified by clinical phenotypes.

Results: The allelic frequency distributions of G at rs3805236 and C at rs1397529 were significantly higher in patients with meningioma than in healthy controls. The frequency of the rs3805236-GG and rs1397529-AC genotypes were significantly higher in patients with meningioma than in controls. Furthermore, there was a statistically significant difference between the genotypes of patients versus healthy individuals at rs1397529, according to stratification by dural invasion. The allelic frequency distributions of alleles or genotypes at rs3805246 and rs3828512 were not different in patients with meningioma and healthy controls.

Conclusions: The Gab1 gene rs3805236A>G and rs1397529A>C SNPs increased the risk of meningioma in the northern Chinese Han population. Furthermore, rs1397529A>C may be related to enhanced dural invasion in patients with meningioma.

Keywords: GAB1 Protein, Human • Meningioma • Polymorphism, Single Nucleotide

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/933444

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Background

Meningiomas are the most common non-glial primary tumor of the central nervous system (CNS), arising from the arachnoidal "cap" cells in the meninges and connected to the dura [1,2]. Meningiomas account for 37.6% of all primary CNS tumors and 53.2% of nonmalignant primary CNS tumors [3]. The incidence of meningioma is 8.83 per 100 000 according to the most recent Central Brain Tumor Registry of the United States and has been increasing in recent years [3-5]. According to the 2016 revision of the World Health Organization (WHO) classification, meningiomas are further categorized into grades I to III: 80% to 90% of cases are WHO I (benign), 20% to 25% are WHO II (atypical), and 1% to 3% are WHO III (anaplastic) [6]. The location and size of a meningioma determine the clinical symptoms, such as headaches, seizures, changes in vision, smell, and hearing, and physical disorders, which severely reduce the life quality of patients. However, there is a lack of an effective biomarker for metastasis prediction and drug target for therapeutic intervention.

Although the etiology and pathogenesis of meningioma remain largely unclear, many studies have verified that the activation of mitogen-activated protein kinases (MAPK) or phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathways are implicated in the pathogenesis of meningioma [7-9]. Presently, the underlying mechanisms of activation of MAPK or PI3K/Akt cascades in meningioma remain unclear.

The growth factor receptor-bound (Grb2)-associated binder (Gab) family of proteins include Gab1, Gab2, and Gab3. Gab1 is the most abundant and widely distributed Gab protein, and Gab3 is mainly expressed in the blood and lymphatic tissues [10-12]. Previous studies have shown that Gab1 prompts cell growth, differentiation, proliferation, migration, and other biological functions mainly through the 2 classical pathways of PI3K/Akt and Ras/MAPK [13-15]. To date, there has been little research on Gab2 or Gab3 in meningioma. However, most studies have confirmed that Gab1 was highly expressed in meningioma [16-18], and the expression might be involved in the invasion of meningioma through the P13K/AKT and Ras/MAPK pathways.

The Gab1 gene is located on chromosome 4, and its single-nucleotide polymorphisms (SNPs) are reported to be closely related to the susceptibility of several human diseases, such as biliary tract cancer and lung cancer [19,20]. The Gab1 SNPs may be involved in the pathogenesis of human diseases by regulating the expression of key genes of disease progression. Whether its genetic SNPs are associated with the risk of meningioma has not yet been reported.

In this study, we genotyped 4 loci of the Gab1 gene and found that Gab1 rs3805236A>G and rs1397529A>C SNPs increased the risk of meningioma in a northern Chinese Han population and the rs1397529A>C SNP may be related to enhanced dural invasion in patients with meningioma. These findings provide a new gene biomarker of meningioma and the basis for our next mechanism research.

Material and Methods

Study Participants

A total of 205 patients with meningioma and 297 healthy controls who were enrolled at the Second Affiliated Hospital of Hebei Medical University from January 2019 to May 2021 were included in this study. No patients with meningioma received radiotherapy or chemotherapy before surgery. Every patient was diagnosed by the Departments of Pathology and Molecular Diagnostics in our hospital according to the 2016 World Health Organization (WHO) classification of CNS tumors [4]. Patients were excluded if they had a history of other tumors, chronic diseases, autoimmune diseases, or endocrine disorders. The study was approved by the Ethics Committee and Institutional Review Board of our hospital. Written informed consent was obtained from each participant.

The study procedure was approved by the Ethics Committee of Hebei Medical University and was in accordance with the principles of the Declaration of Helsinki.

Sample Collection

For each patient and healthy control participant, 5 mL of peripheral venous blood was collected in an EDTA anticoagulant tube. DNA was obtained from the peripheral blood by the standard salting-out procedure and stored at -20°C until use.

Genomic DNA Isolation and SNP Genotyping

The SNPs of Gab1 were selected from the Single-Nucleotide Polymorphism Database of the National Center for Biotechnology Information and the International HapMap Project database with the criteria of linkage disequilibrium value (r^2 >0.8) and minor allele frequency (MAF) >0.1 in the Chinese Han population. Thus, 4 selected sites of Gab1 were tested (rs3805246, rs3828512, rs3805236, and rs1397529). The following were included for further study: rs3805246 G/A (located in chr4: 143382955, intron, G>A), rs3828512 A/G (located in chr4: 143395607, intron, A>G), rs3805236 A/G (located in chr4: 143436584, intron, A>G), rs1397529 A/C (located in chr4: 143471009, 3'UTR, A>C).

Primers were designed using Primer5 and were synthesized by the Sangon Company (Shanghai, China). Following the manufacturer's instructions, genotyping was done using the

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Table 1. Demographic data of the participants for Gab1 single-nucleotide polymorphisms.

Characteristic	Controls (297)	Cases (205)	*P*
Age, mean (SD) year	53.85 (13.30)	55.84 (11.01)	0.068
Gender (M/F)	100 (197)	67 (138)	0.818
Smoking (Y/N)	93 (57)	59 (41)	0.536
Drinking (Y/N)	139 (158)	102 (103)	0.515
Location			
Convexity	NA	86	NA
Cerebral falx	NA	35	NA
Parasagittal	NA	10	NA
Sphenoid wing	NA	16	NA
Anterior skull base	NA	12	NA
Suprasellar	NA	13	NA
Petroclival region	NA	11	NA
Cerebellar tentorium	NA	22	NA
Differentiated degree			
WHO I	NA	150	NA
WHO II	NA	44	NA
WHO III	NA	11	NA

SD – standard deviation; M/F – Male/Female; Y/N – Yes/No; NA – not applicable.

snapshot multiplex assay and analyzed using an ABI 3730XL genetic analyzer. Quality control analysis was performed on the SNPs, and samples that passed the 95% quality threshold were subjected to further statistical analysis.

Statistical Analyses

The distribution of age, sex, smoking status, and drinking status was analyzed by the *t* test or chi-squared test, as appropriate. The chi-squared test and logistic regression were used to evaluate whether allele and genotype frequencies were associated with meningioma susceptibility by analyzing the odds ratio (OR) and 95% confidence interval (CI), adjusted by age and sex. Pairwise linkage disequilibrium and haplotype association analysis were also performed using SHEsis software (*http://analysis2.bio-x.cn/myAnalysis.php*). Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). Where applicable, Bonferroni correction was employed for multiple comparisons. $P<0.05$ was considered statistically significant.

Results

Genotyping and Hardy-Weinberg Equilibrium

Table 1 summarizes the demographic and clinical characteristics of all participants. In total, 205 patients with meningioma and 297 healthy controls were recruited in this study. The mean age was 55.84±11.01 years for the patients and 53.85±13.30 years for the healthy controls. No significant differences were observed in age, sex, smoking history, and alcohol drinking history between the patients and the healthy controls ($P>0.05$).

The goodness-of-fit chi-squared test was used to calculate the Hardy-Weinberg equilibrium (HWE) between healthy controls and patients. The observed genotype and allelic frequency distributions in healthy controls for all SNPs conformed to the Hardy-Weinberg equilibrium ($P_{HWE}>0.05$), which indicated the samples were representative of the population.

Gab1 Gene SNPs Were Correlated with Meningioma Risk

Logistic regression analysis was used to determine the genotype and allele frequencies of the Gab1 SNPs in patients with meningioma and healthy controls under dominant, recessive, and additive models (**Table 2**). Among the 4 SNPs, 2 SNPs (rs3805236 and rs1397529) were significantly associated with a predisposition for meningioma. For Gab1 rs3805236, the frequency of the G allele was higher in the patient group than in the healthy control group ($P=0.001$, OR 1.675, 95% CI 1.252-2.240). The frequencies of the GG homozygote and AG+GG genotype in the patient group were significantly higher than those in the control group (GG: $P=0.002$, OR 3.369, 95% CI 1.704-6.661; AG+GG: $P=0.016$, OR 1.561, 95% CI 1.085-2.246).

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Table 2. Relationship of allele frequencies and genotype distribution of Gab1 single-nucleotide polymorphisms and the risk of meningioma.

SNPs	Genetic model	Allele/ genotype	Controls (n%)	Cases (n%)	*P*	OR (95% CI)	P^{corr}	Adjusted OR (95% CI)
rs3805246		G	468 (78.8)	312 (76.1)	0.314	1.167 (0.864~1.575)	0.258	1.190 (0.880~1.610)
		A	126 (21.2)	98 (23.9)				
	Codominant	GG	189 (63.6)	128 (62.4)	0.216	1 (Reference)	0.183	1
		AG	90 (30.3)	56 (27.3)		0.919 (0.615~1.373)		0.931 (0.622~1.393)
		AA	18 (6.1)	21 (10.2)		1.723 (0.883~3.361)		1.799 (0.918~3.526)
	Dominant	GG	189 (63.6)	128 (62.4)	0.785	1.053 (0.728~1.522)	0.713	1.072 (0.740~1.553)
		AG+AA	108 (36.4)	77 (37.5)				
	Recessive	GG+AG	279 (93.9)	184 (89.8)	0.089	0.565 (0.293~1.090)	0.070	0.543 (0.281~1.052)
		AA	18 (6.1)	21 (10.2)				
	Overdominant	GG+AA	207 (69.7)	149 (72.7)	0.469	1.157 (0.780~1.716)	0.494	1.148 (0.773~1.706)
		AG	90 (30.3)	56 (27.3)				
rs3828512		A	454 (76.4)	304 (74.1)	0.408	0.884 (0.661~1.183)	0.334	0.866 (0.646~1.160)
		G	140 (23.6)	106 (25.9)				
	Codominant	AA	179 (60.3)	122 (59.5)	0.314	1 (Reference)	0.095	1
		AG	96 (32.3)	60 (29.3)		0.917 (0.617~1.363)		0.946 (0.636~1.408)
		GG	22 (7.4)	23 (11.2)		1.534 (0.818~2.875)		2.002 (1.031~3.885)
	Dominant	AA	179 (60.3)	122 (59.5)	0.865	1.032 (0.718~1.484)	0.790	1.051 (0.729~1.513)
		AG+ GG	118 (39.7)	83 (40.5)				
	Recessive	AA+ AG	275 (92.6)	182 (88.8)	0.144	1.580 (0.855~2.918)	0.111	1.654 (0.891~3.071)
		GG	22 (7.4)	23 (11.2)				
	Overdominant	AA+ GG	201 (61.7)	145 (70.7)	0.467	0.866 (0.588~1.276)	0.481	0.870 (0.590~1.282)
		AG	96 (32.3)	60 (29.3)				
rs3805236		A	470 (79.1)	286 (69.8)	0.001	1.643 (1.231~2.194)	0.001	1.675 (1.252~2.240)
		G	124 (20.9)	124 (30.2)				
	Codominant	AA	188 (63.3)	108 (52.7)	0.003	1 (Reference)	0.002	1
		AG	94 (31.6)	70 (34.1)		1.296 (0.878~1.914)		1.288 (0.871~1.906)
		GG	15 (5.1)	27 (13.2)		3.133 (1.597~6.148)		3.369 (1.704~6.661)
	Dominant	AA	188 (63.3)	108 (52.7)	0.018	1.549 (1.079~2.224)	0.016	1.561 (1.085~2.246)
		AG+GG	109 (36.7)	97 (47.3)				

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Table 2 continued. Relationship of allele frequencies and genotype distribution of Gab1 single-nucleotide polymorphisms and the risk of meningioma.

SNPs	Genetic model	Allele/ genotype	Controls (n%)	Cases (n%)	*P*	OR (95% CI)	P^{corr}	Adjusted OR (95% CI)
	Recessive	AA+AG	282 (94.9)	15 (86.8)	0.002	2.852 (1.476~5.509)	0.001	3.074 (1.579~5.983)
		GG	15 (5.1)	27 (13.2)				
	Overdominant	AA+GG	203 (68.4)	135 (65.9)	0.558	1.120 (0.767~1.635)	0.609	1.104 (0.775~1.615)
		AG	94 (31.6)	70 (34.1)				
rs1397529		A	552 (92.9)	364 (88.8)	0.023	0.602 (0.388~0.934)	0.028	0.609 (0.392~0.947)
		C	42 (7.1)	46 (11.2)				
	Codominant	AA	255 (85.9)	159 (77.6)	0.017	1.757 (1.106~2.790)	0.020	1.737 (1.090~2.768)
		AC	42 (14.1)	46 (22.4)				

OR – odds ratios; CI – confidence intervals; Adjusted OR – data was adjusted for gender and age; P^{corr} – corrected *P* values by Bonferroni correction, adjusted by age and gender.

For Gab1 rs1397529, patients with meningioma showed significantly higher frequencies of the rs1397529 C allele (11.2%) than did healthy controls (7.1%) (OR 0.602, 95% CI 0.388-0.934, *P*=0.023, P^{corr}=0.028). Under the codominant model, the heterozygous AC genotype of rs1397529 was associated with a high risk of meningioma, compared with the wild AA genotype (OR 1.737, 95% CI, 1.090-2.768, P^{corr}=0.020). With respect to Gab1 rs3805246 and rs3828512, there were no differences in the genotype distribution and allele frequencies between patients with meningioma and healthy controls (*P*>0.05, **Table 2**).

Linkage Disequilibrium and Haplotype Analyses

Linkage disequilibrium and haplotype analyses of the SNPs in the patient and healthy control samples were further studied. Linkage disequilibrium relationships between SNPs evaluated using the r^2 measure. In **Figure 1**, the graphical representation generated by SHEsis of the r^2 linkage disequilibrium relationship between each SNP is expressed in different colors, where deep red represents high linkage disequilibrium (r^2 >0.80) and light red represents low linkage disequilibrium (r^2 <0.80). However, the linkage disequilibrium was not strong enough to create any haplotype blocks; therefore, we were not able to perform a haplotype analysis.

Stratification Analyses Were Performed According to the Clinical Features

Patients were stratified according to tumor size, status, location, WHO grade, peritumoral edema, and dural invasion status. Tumor size, status, location, WHO grade, and peritumoral edema were not associated with the sites. However, the rs1397529 AC frequencies were determined to be higher in patients with

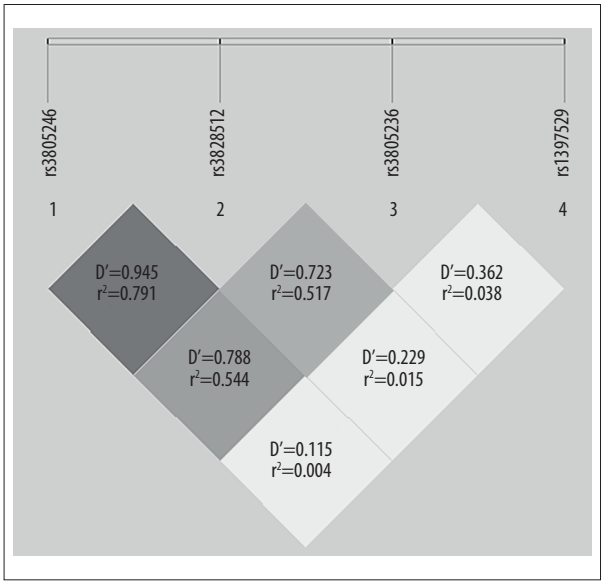

Figure 1. Linkage disequilibrium map of 4 selected loci of the Gab1 gene.

meningioma with dural invasion (*P*=0.027, **Table 3**). This may indicate that the SNP of rs1397529 on Gab1 increased the risk of meningioma development and might facilitate dural invasion in patients with meningioma.

Discussion

It has been shown that Gab1 is highly expressed in meningioma, and its downstream signaling pathways have recently been implicated in human meningioma pathogenesis [16-18]. However, the association of the Gab1 SNPs and meningioma

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Table 3. Stratification analysis between Gab1 single-nucleotide polymorphisms and the clinical characteristics of meningioma.

Clinical characteristics (n)	rs3805246			rs3828512			rs3805236			rs1397529		
	GG	AG+GG	P	AA	AG+GG	P	AA	AG+GG	P	AA	AC	P
Tumor size (cm)												
d ≤4.5 (109)	66	43	0.552	62	47	0.413	56	53	0.690	87	22	0.409
d >4.5 (96)	62	34		60	36		52	44		72	24	
Location												
Convexity (87)	51	36	1.559	48	39	2.807	41	46	1.894	63	24	2.385
Skull basis (66)	41	25		38	28		37	29		54	12	
Others (52)	36	16		35	17		29	23		42	9	
WHO grade												
I (150)	97	53	0.277	92	58	0.380	79	71	0.994	115	35	0.612
II+III (55)	31	24		30	25		29	26		44	11	
Peritumoral edema												
Yes (120)	80	40	0.138	76	44	0.185	63	57	0.950	91	29	0.481
No (85)	48	37		46	39		45	40		68	17	
Dural invasion												
Yes (91)	59	32	0.527	56	35	0.597	49	42	0.766	64	27	0.027
No (114)	69	45		66	48		59	55		95	19	

risk has not been reported. In our study, we found 2 loci (rs1397529 and rs3805236) were significantly associated with meningioma risk. The distributions of genotypes and alleles of Gab1 rs1397529 and rs3805236 were significantly different between patients with meningioma and healthy controls. For rs1397529, logistic regression analysis showed that the MAF of rs1397529 on the Gab1 gene was significantly higher in patients with meningioma than in healthy controls, suggesting that the C allele elevated the risk of meningioma and the higher heterozygous AC genotype on rs1397529 increased the risk of meningioma in the Chinese Han population. For rs3805236, the G allele of rs3805236 was also higher in meningioma and might be another risk allele of meningioma. Also, the GG homozygote on rs3805236 increased the risk of meningioma in our study. However, no strong linkage disequilibrium relationship between rs1397529 and rs3805236 was observed. Furthermore, there was a statistically significant relationship between the genotypes at rs1397529, as revealed by stratification analysis of dural invasion, suggesting that the AC genotype was significantly more aggressive than the AA genotype in patients with meningioma. The stratification analysis by dural invasion indicated that the SNP of rs1397529 on Gab1 increased the risk of meningioma development, and might have also facilitated dural invasion in patients with meningioma.

Gab1 SNPs have been found to increase the risk of a number of human diseases [14,19-21]. A previous study showed that the Gab1 rs3805246 AA genotype was associated with a low risk of *Helicobacter pylori* infection, while AG and AA genotypes might increase the risk of chronic atrophic gastritis in the Japanese population [21]. However, the Gab1 rs3805246 SNP was not significantly related to the susceptibility to *H. pylori* infection and chronic atrophic gastritis among older adults in Germany [14]. Meng et al conducted a case-control study about the same loci in the Han population of Northeast China and showed that the MAF of rs3805246 was higher in the case group (42.0%) than in the control group (34.5%) and the A allele and AA genotype were a risk factor for biliary tract cancer [19]. In the present study, we did not find a correlation between this loci and meningioma risk in the northern Chinese Han population, and the MAF in the control group was the only result in our study that was similar to that of Meng et al. The differences can be due to several reasons. First, it may be due to a different genetic background, such as frequencies of the AA genotype at rs3805246. Also, different environmental factors can potentially induce various gene modifications [22,23]. Furthermore, gene SNPs differ in individual populations, regions, and races or ethnicities [24,25].

We found that Gab1 rs3805236 was linked to an increased risk of meningioma; in other words, rs3805236 G was a risk factor

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for meningioma. Meng reported that the Gab1 rs3805236 gene SNP was not associated with biliary tract cancer susceptibility in the Liaoning Han population [19]. However, our study has some similarities to Meng's study. The GG genotype frequencies in the control groups of both studies were similar (5.1% vs 6.0%). Also, the genotypes of rs3805236 in the control groups conformed to Hardy-Weinberg equilibrium in both studies (P>0.01). The results that differ could be attributed to the fact that SNPs can generate diverse effects in individuals for different diseases [26].

In the present study, we found that rs1397529 C alleles were risk factors for meningioma. Li et al reported that the MAF of rs1397529 was significantly lower in the case group (5.8%) than in the control group (8.2%); the C allele was a protective factor, and a dominant genetic model of rs1397529 was associated with a reduced risk of lung cancer, compared with the AA genotype in a previous study [20]. We found 2 genotypes (AA and AC) at this locus, while 3 genotypes (AA, AC, and CC) were found in the study by Li et al. The CC genotype in the latter was only 0.8%. The variation may be attributed to a relatively small sample size in our study; however, we achieved a statistical power of 85%. Few studies have investigated the relationship of the Gab1 gene SNPs and meningioma risk in other populations. Therefore, further studies of these SNPs in a larger sample size should be conducted.

According to the stratified dural invasion analysis, there was a significant difference in the genotypes of patients with meningioma at rs1397529. This may indicate that rs1397529 plays a role in meningioma. The rs1397529 site is located in the 3'UTR of Gab1. It has been shown that the main functions of SNPs in 3'UTR are related to the regulation of DNA transcription and the subsequent gene translation and tissue-specific expression. The same gene expression may differently affect the separate cell behaviors through different signaling pathways. 3'UTR is an essential regulatory region for the expression of many genes that regulate the translation, degradation, and subcellular localization of mRNAs by influencing RNA-binding proteins or non-coding RNAs [27,28]. 3'UTR SNPs can significantly impact gene expression by abolishing, weakening, or creating miRNA binding sites [29,30]. The results of the present study indicated that the rs1397529 C allele may facilitate dural invasion in patients with meningioma through regulating 3'UTR of the Gab1 gene and may ultimately influence Gab1 transcription or translation.

Several studies have documented that Gab1 can promote the growth, migration, and invasion of tumor cells through MAPK or PI3K/Akt signaling pathways [31-34]. It seems that decreased MAPK activity was related to the recurrence of meningioma and PI3K activation was related to poor preclinical conditions and brain invasion of malignant meningioma [7]. The expression of phosphorylated Raf and MAPK is reduced in aggressive meningioma; however, inhibition of MAPK leads to reduced tumor cell apoptosis and proliferation [9]. Our results indicated that the rs1397529 C allele may facilitate dural invasion in patients with meningioma through affecting the regulation of the 3'UTR of the Gab1 gene, ultimately influencing Gab1 transcription or translation. In view of findings from published studies and our experimental data, we further speculated that the genetic SNPs in Gab1 may functionally regulate protein expression through the P13K/AKT or MAPK pathway to affect the growth, proliferation, and invasion characteristics of meningioma.

There are limitations to this study. Although we identified the association between the Gab1 SNPs and meningioma risk, further investigations are needed in a larger and more ethnically diverse population of patients with meningioma to confirm our conclusions. Also, patients with meningioma with certain diseases were excluded from our study to maintain the homogeneity of samples; however, the Gab1 genotypes that are inversely associated with these diseases may have been excluded.

Conclusions

In the present study, we were the first researchers to find that the Gab1 gene rs3805236A>G and rs1397529A>C SNPs were associated with meningioma susceptibility in the northern Chinese Han population and that rs1397529A>C may be related to enhanced dural invasion in patients with meningioma. These findings provide a new gene biomarker of meningioma and the basis for our future mechanism research.

Ethics Approval and Consent to Participate

All participants voluntarily joined the study and provided written informed consent. The protocol of this study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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