Impact of AKAP6 Polymorphisms on Glioma Susceptibility and Prognosis

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Abstract

Purpose

Glioma is the most common primary malignant brain tumor with high mortality and poor prognosis. Our aim was to clarify the correlation between AKAP6 gene polymorphisms and glioma susceptibility and prognosis in Chinese Han population.

Methods

Five single-nucleotide polymorphisms (SNPs) of AKAP6 were genotyped by Agena MassARRAY in 575 glioma patients and 500 healthy controls. Logistic regression model was utilized to calculate odds ratios (OR) and 95% confidence intervals (CI). The associations between polymorphisms and survival were assessed using the log-rank test, Kaplan-Meier analysis and Cox regression model.

Results

We found that rs2239647 polymorphism was strongly associated with an increased risk of glioma (OR = 1.90, p = 0.007) and a worse prognosis for glioma, especially in high-grade glioma (HR = 1.67, p = 0.034). Stratified analysis showed that rs2239647 increased the risk of glioma in female (OR = 1.62, p = 0.016). Whereas, rs4261436 (HR = 0.70, p = 0.045) and rs17522122 (HR = 0.75, p = 0.016) were associated with better prognosis of astrocytoma. In addition, we also found that surgical methods and chemotherapy are critical factors for the prognosis of glioma patients.

Conclusions

This study firstly provided evidence for the impact of AKAP6 polymorphisms on susceptibility and prognosis of glioma, suggesting AKAP6 variants might have potential roles in the etiology of glioma.

Background
Glioma is the most common primary brain tumor, accounting for about 80% of malignant brain tumors[1, 2]. Gliomas are often fatal because many drugs that are effective against tumors throughout the body cannot cross the blood-brain barrier. Despite advances in treatment over the past few years, the prognosis for glioma patients remains poor, with a median overall survival rate (OS) of only 8 to 15 months[3, 4]. The etiology of glioma involves various aspects, among which the role of genetic factors including genetic polymorphisms in the susceptibility and prognosis of glioma has aroused great concern. Single nucleotide polymorphisms of some genes have been shown to be associated with the risk or prognosis of glioma, such as IL-4R, EFEMP1, RTEL1, CART and IDH1[5-9]. Kinase-anchored protein 6 (AKAP6), encoded by the AKAP6 gene, is a protein with diverse structures and is highly expressed in various brain regions and cardiac and skeletal muscle. AKAP6 is a member of the AKAP family proteins and performs important functions by binding to the regulatory subunit of protein kinase a (PKA)[10]. PKA has been shown to be involved in many important signal transduction pathways. A previous study demonstrated effects of up-regulation of the cAMP/PKA pathway in glioblastoma cell[11]. Genome-wide association studies (GWAS) have confirmed that the SNPs of AKAP6 were associated with brain-related diseases, such as Alzheimer's disease[12], anorexia nervosa[13], and poor cognitive, better memory abilities[14]. Based on previous results, we hypothesized that AKAP6 gene polymorphisms may be related to the pathogenesis of glioma. However, no literature supports the effect of AKAP6 polymorphisms on glioma. In this case-control study, we investigated the correlation between AKAP6 single nucleotide polymorphisms and glioma susceptibility and prognosis in the Han Chinese population.

Methods

Study subjects
In this study, 575 glioma patients (including 448 patients with astroglioma) and 500 healthy subjects were randomly recruited from Second Affiliated Hospital of Xi’an Jiaotong University. All patients were diagnosed with gliomas by imaging and histopathological, and all patients were unrelated. Peripheral blood of the patients was collected before receiving treatment. Demographic and clinical data were collected through standardized questionnaires and follow-up surveys, including age, sex, date of the first diagnosis, method of surgery, radiotherapy and/or chemotherapy program, date of last follow-up, and the condition of the patient (alive/dead) at the time of the last follow-up. Healthy subjects in the control group ruled out people with a history of cancer and people with a history of diseases associated with the brain and central nervous system. This study was approved by the ethics committee of Second Affiliated Hospital of Xi’an Jiaotong University and followed the Helsinki declaration. Each subject was informed of the purpose of our study and signed a written informed consent.

**DNA extracting and SNPs genotyping**

Genomic DNA was extracted from glioma patients’ peripheral blood samples (5 mL) using Gold Mag-Mini DNA purification kit (Gold Mag Co. Ltd. Xian city, China). DNA concentrations were determined by the NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA). Multiplexed SNP Mass EXTENDED assay was designed by Agena MassARRAY Assay Design Software version 4.0 (Agena Co. Ltd., San Diego, CA, USA). SNP genotyping with a standard protocol was performed using Agena MassARRAY RS1000 (Agena Inc., San Diego, CA, USA). Agena Typer Software version 4.0 (Agena Inc., San Diego, California, USA) was used to management the data.

**Bioinformatics analysis**

Online software for HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) and SNPinfo Web Server (https://snpinfo.
Statistical analysis

The differences in demographic characteristics of study participants were evaluated using independent samples T test and Chi-square test. Deviation from Hardy-Weinberg equilibrium (HWE) was assessed using the Chi-square test. Odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate the relationships between SNPs and glioma risk using logistic regression analysis. Multiple inheritance models (allele model, genotype model, dominant model, recessive model, and additive model) were assessed by PLINK software. Patient survival curves were plotted using the Kaplan-Meier method, and the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated through univariate and multivariable Cox proportional hazard regression analysis to evaluate the effect of the AKAP6 genotypes on overall survival and progression-free survival[15-17]. Statistical analysis was performed using SPSS Software version 20.0 (IBM, Armonk, New York, USA). A two-tailed $p < 0.05$ was considered statistical significance.

Discussion

Study subjects

This study included 575 glioma patients and 500 age-matched ($p = 0.942$) and gender-matched ($p = 1.000$) healthy controls, and the average ages were $40.53 \pm 13.90$ years and $40.45 \pm 18.08$ years respectively. The participants' demographic and clinical information was listed in Table 1, including age, gender, WHO grade and classification, surgical method, radiotherapy, chemotherapy and survival condition.

Basic information of the selected SNPs

Five SNPs in AKAP6 (rs1957021, rs2145587, rs2239647, rs4261436 and rs17522122) were genotyped. The basic information of selected SNPs and potential function predicted by
HaploReg database about these variants were summarized in Supplementary Table 1. All SNPs conformed to the HWE equilibrium (all $p$ values were more than 0.05). The predicted results from the database showed that these SNPs might function as enhancer histone markers or by changing motifs.

**The SNPs of AKAP6 and the risk of glioma**

Multiple inheritance models analysis (allele, genotype, dominant, recessive and additive) for the association between AKAP6 rs2239647 and risk of glioma are showed in Table 2. Our analysis revealed a relationship between AA genotype of rs2239647 and increased glioma risk in genotype model ($OR = 1.88$, 95% CI: 1.16-3.04, $p = 0.010$) and recessive model ($OR = 1.90$, 95% CI: 1.19-3.03, $p = 0.007$).

In addition, we conducted a stratified analysis to explore the effects of these SNPs on glioma susceptibility in a specific population. The significant results of stratified analysis are showed in Table 3. The results showed that AA genotype at rs2239647 was significantly associated with increased glioma risk in populations over than 40 years old (genotype model: $OR = 2.60$, $p = 0.012$; recessive model: $OR = 2.83$, $p = 0.006$) and in the male population (genotype model: $OR = 2.42$, $p = 0.003$; recessive model: $OR = 2.49$, $p = 0.009$). And, people with the rs2239647-AA genotype had a higher risk of astroglioma than healthy controls (genotype model: $OR = 1.90$, $p = 0.012$; recessive model: $OR = 1.92$, $p = 0.009$). Moreover, rs2145587 was associated with an increased risk of glioma in female (genotype model: $OR = 1.62$, $p = 0.016$; dominant model: $OR = 1.57$, $p = 0.017$).

**Analysis of the prognostic of glioma**

The log-rank test was applied to analyze the associations between overall survival (OS) or progression free survival (PFS) and clinical factors, and the results indicated that gender, age, WHO grading, and radiotherapy factors were not related to the prognosis of patients ($p > 0.05$), while surgical methods and chemotherapy were significantly related to the
prognosis of patients \( p < 0.05 \) (Supplement table 2 and Supplement Fig. 1). We found that the prognosis of glioma patients undergoing total resection was better than patients who did not undergo complete resection (OS: log-rank \( p < 0.001 \), HR = 0.63, \( p < 0.001 \); PFS: log-rank \( p < 0.001 \), HR = 0.59, \( p < 0.001 \)). The prognosis of patients receiving chemotherapy was better than that of patients not receiving chemotherapy (OS: log-rank \( p < 0.001 \), HR = 0.67, \( p < 0.001 \); PFS: log-rank \( p = 0.012 \), HR = 0.81, \( p = 0.025 \)).

We evaluated the effect of \textit{AKAP6} polymorphisms on the patient survival. Log-rank test and Kaplan-Meier analysis revealed the relationship between rs2239647 and OS and PFS in glioma patients (Table 4 and Fig. 1). We found that \textit{AKAP6}-rs2239647 significantly affected the PFS of patients with high-level glioma (WHO grade III–IV), and patients with CA genotype had a better prognosis (PFS: log-rank \( p = 0.045 \), HR = 1.67, \( p = 0.034 \)).

Subsequently, we analyzed the effect of \textit{AKAP6} polymorphisms on the prognosis of patients with astroglia (Table 5 and Fig. 2). The results showed that \textit{AKAP6}-rs4261436 had a significant effect on the OS of patients, and patients with TC genotype had a poor prognosis (OS: log-rank \( p = 0.038 \), HR = 0.70, \( p = 0.045 \)). \textit{AKAP6}-rs17522122 also had a significant effect on the OS of patients, and patients with TC genotype had a poor prognosis (OS: log-rank \( p = 0.025 \), HR = 0.75, \( p = 0.016 \)).

**Conclusions**

In summary, our results show that \textit{AKAP6} polymorphism is associated with the susceptibility and prognosis of glioma in the Chinese Han population. These associations may provide new directions for risk assessment of glioma and prognosis assessment of glioma patients. However, our results need to be replicated in a larger sample size and validated by functional experiments.

**Declarations**
Acknowledgments

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Declaration of interest statement

The authors declare that they have no conflict of interest.

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Tables

Table 1 Characteristics of glioma patients and healthy controls
### Characteristics of Cases and Controls

| Characteristics | Cases (n = 575) | Controls (n = 500) | p |
|-----------------|----------------|-------------------|---|
| Age, years      | Mean ± SD (year) | 40.53 ± 13.90     | 40.45 ± 18.08 | 0.942<sup>a</sup> |
|                 | ≤ 40            | 279 (49%)         | 265 (53%)     | |
|                 | > 40            | 296 (51%)         | 235 (47%)     | |
| Gender          | Male            | 320 (56%)         | 279 (56%)     | 1.000<sup>b</sup> |
|                 | Female          | 255 (44%)         | 221 (44%)     | |
| WHO grade       | I-II            | 369 (64%)         | 206 (36%)     | |
|                 | III-IV          | 448 (78%)         |               | |
| astrocytoma     | STR & NTR       | 184 (32%)         |               | |
| Surgical method | GTR             | 394 (68%)         |               | |
| Radiotherapy    | Gamma knife     | 365 (63%)         |               | |
|                 | Conformal radiotherapy | 156 (27%) |               | |
| Chemotherapy    | Yes             | 237 (41%)         |               | |
|                 | No              | 341 (59%)         |               | |
| State of progress | Progress      | 538 (93%)         |               | |
|                 | No              | 5 (1%)            |               | |
|                 | Absent          | 5 (1%)            |               | |

WHO: World Health Organization; GTR, Gross-total resection; NTR, Near-total resection; STR, Sub-total resection.

<sup>a</sup> p values was calculated by independent samples T test.

<sup>b</sup> p values was calculated by Chi-square tests.

### Table 2: Relationships between AKAP6 rs2239647 and glioblastoma risk

| SNP ID    | Model       | Genotype | Case | Control | Adjusted by age and gender | OR (95%CI) | p   |
|-----------|-------------|----------|------|---------|----------------------------|------------|-----|
| rs2239647 | Allele      | C        | 817  | 746     | 1.00                       | 1.18 (0.98-1.43) | 0.086 |
|           |             | A        | 329  | 254     | 1.00                       | 0.98 (0.76-1.26) | 0.849 |
|           | Genotype    | CC       | 302  | 274     | 1.00                       | 1.88 (1.16-3.04) | 0.010 |
|           |             | CA       | 213  | 198     | 1.00                       | 1.09 (0.85-1.38) | 0.494 |
|           | Dominant    | CC       | 302  | 274     | 1.00                       | 1.90 (1.19-3.03) | 0.007 |
|           |             | CA-AA    | 271  | 226     | 1.00                       | 1.18 (0.97-1.42) | 0.091 |
|           | Recessive   | CC-CA    | 515  | 472     | 1.00                       |             |     |
|           |             | AA       | 58   | 28      | 1.00                       |             |     |
|           | Additive    | ---      | ---  | ---     | 1.00                       |             |     |

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SNP: single nucleotide polymorphism; OR: odds ratio; 95% CI: 95% confidence interval.

$p$ values were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ means the data is statistically significant.

Table 3 Stratified analysis of the relationships between $AKAP6$ polymorphisms and glioma risk
| SNP ID   | Models            | OR (95%CI) | p   | OR (95%CI) | p   |
|----------|-------------------|------------|-----|------------|-----|
|          | Age               | ≤ 40       | > 40|            |     |
|          |                   |            |     |            |     |
| rs2239647| Allele            | 1.20 (0.92-1.57) | 0.171 | 1.17 (0.89-1.54) | 0.273 |
|          | Homozygote(AA)    | 1.68 (0.87-3.24) | 0.123 | 2.60 (1.23-5.51) | 0.012 |
|          | Heterozygote(CA)  | 1.19 (0.83-1.71) | 0.347 | 0.82 (0.57-1.18) | 0.281 |
|          | Dominant          | 1.26 (0.89-1.78) | 0.187 | 0.98 (0.70-1.39) | 0.925 |
|          | Recessive         | 1.56 (0.82-2.95) | 0.174 | 2.83 (1.36-5.89) | 0.006 |
|          | Additive          | 1.25 (0.95-1.64) | 0.107 | 1.17 (0.89-1.54) | 0.254 |
|          |                   |            |     |            |     |
| Gender   | Allele            | 1.06 (0.84-1.33) | 0.633 | 1.28 (0.98-1.68) | 0.065 |
|          | Homozygote(AA)    | 1.16 (0.71-1.90) | 0.553 | 1.40 (0.77-2.53) | 0.266 |
|          | Heterozygote(CA)  | 1.00 (0.70-1.43) | 0.998 | 1.62 (1.10-2.38) | 0.016 |
|          | Dominant          | 1.04 (0.74-1.45) | 0.837 | 1.57 (1.08-2.27) | 0.017 |
|          | Recessive         | 1.16 (0.74-1.82) | 0.514 | 1.08 (0.62-1.87) | 0.794 |
|          | Additive          | 1.06 (0.84-1.34) | 0.625 | 1.30 (0.99-1.71) | 0.060 |
|          |                   |            |     |            |     |
| rs2239647| Allele            | 1.22 (0.94-1.58) | 0.130 | 1.14 (0.86-1.51) | 0.374 |
|          | Homozygote(AA)    | 2.42 (1.21-4.87) | 0.003 | 1.48 (0.75-2.89) | 0.256 |
|          | Heterozygote(GA)  | 0.94 (0.67-1.32) | 0.714 | 1.02 (0.70-1.50) | 0.909 |
|          | Dominant          | 1.08 (0.78-1.50) | 0.627 | 1.09 (0.76-1.57) | 0.630 |
|          | Recessive         | 2.49 (1.25-4.93) | 0.009 | 1.46 (0.76-2.80) | 0.253 |
|          | Additive          | 1.22 (0.94-1.57) | 0.135 | 1.13 (0.86-1.50) | 0.384 |
|          |                   |            |     |            |     |
| Classification | Astroglioma patients VS Healthy controls | | | | |
| rs2239647| Allele            | 1.18 (0.96-1.45) | 0.106 |       |     |
|          | Homozygote(AA)    | **1.90 (1.15-3.15)** | **0.012** |       |     |
|          | Heterozygote(CA)  | 0.98 (0.75-1.29) | 0.900 |       |     |
|          | Dominant          | 1.10 (0.85-1.42) | 0.485 |       |     |
|          | Recessive         | **1.92 (1.17-3.13)** | **0.009** |       |     |
|          | Additive          | 1.19 (0.97-1.45) | 0.098 |       |     |

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

*p values were calculated by logistic regression analysis with adjustments for age and*
p < 0.05 indicates statistical significance.

Table 4 The association between rs2239647 and glioma patient OS and PFS

| rs2239647 | Genotype | Log-rank p | SR (1-3-year) | HR (95%CI) | p | Log-rank p | SR (1-3-year) | HR (95%CI) | p |
|-----------|----------|------------|---------------|------------|---|------------|---------------|------------|---|
| CC        | 0.227    | 0.328/0.080| 1.00          | 0.346      | 0.413 | 0.182/0.084| 1.00         |
| CA        | 0.327/0.134| 1.15 (0.86-1.54) | 0.193/0.122 | 1.13 (0.84-1.51) | 0.424 |
| AA        | 0.224/0.034| 0.91 (0.76-1.10) | 0.138/0.039 | 0.94 (0.78-1.13) | 0.517 |

Low-grade glioma(I-II)

| CC        | 0.124    | 0.324/0.077| 1.00          | 0.267 | 0.159/1.00 |
| CA        | 0.349/0.165| 0.96 (0.66-1.39) | 0.232/0.147 | 0.93 (0.64-1.35) | 0.686 |
| AA        | 0.270/-  | 0.80 (0.64-1.01) | 0.189/- | 0.84 (0.66-1.06) | 0145 |

High-grade glioma(III-IV)

| CC        | 0.056    | 0.333/0.085| 1.00          | 0.045 | 0.219/0.092| 1.00         |
| CA        | 0.279/-  | 1.61 (1.04-2.66) | 0.106/- | 1.67 (1.04-2.67) | 0.034 |
| AA        | 0.143/-  | 1.19 (0.87-1.63) | 0.048/- | 1.21 (0.88-1.66) | 0.233 |

OS: Overall survival; PFS: Progression free survival; SR: Survival rate; HR: Hazard ratio; 95% CI: 95% Confidence interval.

Log-rank p values were calculated using the Chi-Square test.

p < 0.05 indicates statistical significance.

Table 5 The association between rs4261436, rs17522122 and astrocytoma patient OS and PFS
| SNP ID | Genotype | Log-rank *p* | OS SR (1-/3-year) | HR (95%CI) | Log-rank *p* | PFS SR (1-/3-year) | HR (95%CI) |
|--------|----------|--------------|--------------------|------------|--------------|--------------------|------------|
| rs426 1436 | TT       | **0.038**    | 0.258/0.033       | 1.00       | 0.176        | 0.152/1.00        |            |
|         | TC       |              | 0.367/0.116       | **0.70** (0.49-0.99) | 0.178/- | 0.75 (0.53-1.07) | 0.116      |
|         | CC       |              | 0.356/0.111       | 0.81 (0.64-1.02) | 0.267/- | 0.88 (0.70-1.12) | 0.308      |
| rs175 22122 | GG      | **0.025**    | 0.268/0.049       | 1.00       | 0.053        | 0.137/-           | 1.00       |
|         | GT       |              | 0.352/0.106       | **0.75** (0.59-0.95) | 0.190/- | 0.79 (0.55-1.13) | 0.686      |
|         | TT       |              | 0.341/0.042       | 0.78 (0.54-1.12) | 0.268/- | 0.78 (0.62-0.99) | 0.038      |

OS: Overall survival; PFS: Progression free survival; SR: Survival rate; HR: Hazard ratio;

95% CI: 95% Confidence interval.

Log-rank *p* values were calculated using the Chi-Square test.

*p* < 0.05 indicates statistical significance.

Figures
Figure 1

Glioma patient survival based on AKAP6-rs2239647 polymorphism. Kaplan-Meier survival curves are plotted for and progression free survival.
Figure 2

Astrogloma patient survival based on AKAP6-rs4261436 and -rs17522122 polymorphisms. Kaplan–Meier survival curves are plotted for overall survival.

Supplementary Files

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