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# Association between genetic polymorphisms of *PTGS2* and glioma in a Chinese population

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**ABSTRACT.** Several previous studies indicated that genetic polymorphisms in inflammatory factor genes were associated with glioma risk. However, the relationship between the prostaglandin-endoperoxide synthase 2 (*PTGS2*) genetic polymorphism and glioma remains unclear in the Chinese population. We selected 199 histologically confirmed adult glioma patients and 199 cancer-free controls for the present study and analyzed the distribution of the *PTGS2* genotypes and haplotypes. We found that the CC+CT genotype of rs5275 was common in the control group but not in the glioma group (P = 0.033). In addition, we found that the frequency of the C allele was higher in the control group than in the glioma group (P = 0.014). For rs6681231, although we found no significant difference between the 2 groups in genotype distribution, we found that the frequency of the C allele was lower in glioma patients than in control subjects (P = 0.044). We found no significant difference between these 2 groups in the rs689466 genotype and allele distributions. Haplotype analysis suggested that the frequency of the C-A-C haplotype was significantly lower in glioma patients than in control subjects [P = 0.028, odds ratio

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(OR) = 0.628, 95% confidence interval (CI) = 0.413-0.955]. However, the frequency of the T-A-G haplotype was higher in glioma patients than in control subjects (P = 0.036, OR = 1.418, 95%CI = 1.022-1.967). Therefore, polymorphisms in the *PTGS2* gene may be associated with glioma susceptibility in the Chinese population.

**Key words:** Genetic polymorphism; Glioma; *PTGS2*

## INTRODUCTION

Glioma, the most common type of brain tumor worldwide, has an incidence rate of approximately 6 in 100,000 people annually. Previous studies have suggested that the 5-year survival rate of glioma patients is approximately 20% (Amirian et al., 2010; Okada et al., 2013). Therefore, it is very important to identify the factors leading to the development of glioma. Various studies have indicated that risk factors such as exposure to ionizing radiation (Liu et al., 2013), genetic polymorphisms (Amirian et al., 2010; Liang et al., 2013; Zeybek et al., 2013; Cheng et al., 2013), and family history of cancer (Goodenberger and Jenkins, 2012) are associated with glioma.

Previous studies have also indicated that allergic or inflammatory reactions were inversely associated with glioma risk (Turner et al., 2013; Schebesch et al., 2013). In the brain, the anti-inflammatory properties of interleukin-4 and interleukin-13 are likely based on their abilities to enhance cyclooxygenase (COX)-2 expression, causing cell death of activated microglia (Chen et al., 2012). Several studies have demonstrated that COX-2 expression is associated with glioma angiogenesis (Jankovsky et al., 2013; Erdem et al., 2013). Sivak-Sears et al. (2004) reported an inverse association between nonsteroidal anti-inflammatory drug use and glioblastoma risk, which is consistent with the results of other studies. COX-2 is encoded by the prostaglandin-endoperoxide synthase 2 (*PTGS2*) gene. Single nucleotide polymorphisms (SNPs) in *PTGS2* have been reported to be associated with the risk of various cancers, such as prostate cancer (Jhang et al., 2013), breast cancer (Thorat et al., 2013), and bladder cancer (Bhattacharya et al., 2013). However, the role of such SNPs in the *PTGS2* gene on the risk of glioma remains unclear.

We performed a case-control study to determine the relationship between *PTGS2* genetic polymorphisms and the risk of glioma in a Chinese population.

## MATERIAL AND METHODS

### Subjects

This study was approved by the Ethics Committee of the First People's Hospital of Shenyang. All participants signed inform consent forms before participating in the study. Glioma patients and control subjects were enrolled in the First People's Hospital of Shenyang between July 2001 and July 2013. For the glioma patients, we initially identified 212 subjects diagnosed with glioma (International Classification of Disease, Oncology, Third Edition [ICD-O-3] morphology codes 9380-9411, 9420-9480, and 9505). We subsequently excluded 13 case subjects diagnosed with medulloblastoma or primitive neuroectodermal tumor (ICD-O-3 codes 9470-9474). A total of 199 glioma patients were included in the present study, of

which 123 were males and 76 were females, aged 25-74 years (mean, 63 ± 11.3 years). A total of 199 control subjects were matched to case subjects within a 2-year age interval and for gender. Control subjects were also required to be alive and free from any cancer.

## Genotyping

We performed a haplotype-based case-control study; therefore, we genotyped the tag-SNPs of *PTGS2*. We utilized the Haploview 4.2 software based on the HapMap phase II database and obtained 3 tagging SNPs (rs6681231, rs5275, and rs689466) for Han Chinese with minor allele frequency ≥0.15 and $r^2 \geq 0.8$ (Figure 1).

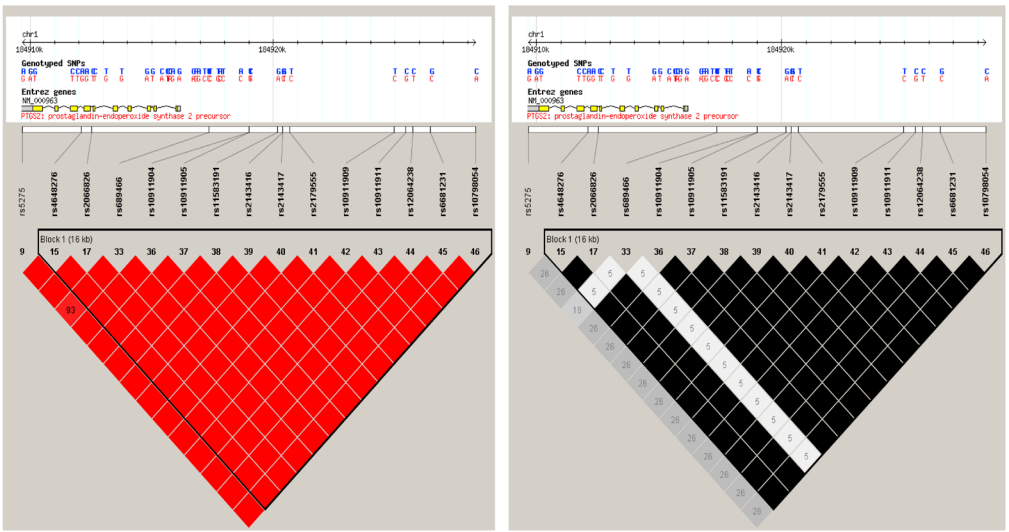


**Figure 1.** Genetic variation at the human *PTGS2* gene. Using the Haploview 4.2 software and the HapMap phrase II database, we scanned 15 genotyped single nucleotide polymorphisms (SNPs) in Chinese Han. Linkage disequilibrium (LD) blocks across the locus in Chinese Han. LD block derived by solid spline method in Haploview 4.2. LD value shown: (**A**) |D'| x 100; |D'| color scheme: |D'| = 0: white; 0 < |D'| < 1: shades of pink; |D'| = 1: red; (**B**) $r^2$ x 100; $r^2$ color scheme: $r^2 = 0$: white; $0 < r^2 < 1$: shades of gray; $r^2 = 1$: black

Genomic DNA was extracted from peripheral blood leukocytes using a DNA extraction Kit (Beijing Bioteke Co. Ltd., Beijing, China). Genotyping was confirmed using the TaqMan method as described by Xie et al. (2009, 2011).

## Statistical analyses

The SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA) was utilized to perform data analysis. We utilized the $\chi^2$ test to assess Hardy-Weinberg equilibrium and to compare the difference between the case and control groups regarding the allele and genotype distribution. We calculated the odds ratios (ORs) and 95% confidence intervals (95%CIs) using unconditional

logistic regression. The SHEsis software was utilized to perform linkage disequilibrium analysis and haplotype analysis. Haplotypes with a frequency of <0.02 were excluded. Statistical significance was established at $P < 0.05$.

## RESULTS

### Subjects and general characteristics

A total of 398 subjects were recruited in this case-control study, including 199 glioma patients and 199 cancer-free controls. The clinical characteristics of these 2 groups are shown in Table 1. There were no significant differences between glioma patients and cancer-free controls in terms of age, gender, alcohol consumption, and smoking (all $P > 0.05$).

**Table 1.** Clinical characteristics of glioma cases and controls.

| Characteristics | Cases [N (%)] | Controls [N (%)] | P value |
|---|---|---|---|
| Number | 199 | 199 | |
| Gender (male) | 123 (61.8) | 126 (63.3) | 0.676 |
| Age (years) | 63 ± 11.3 | 64 ± 10.7 | 0.776 |
| Smoking | 125 (63.3) | 118 (59.3) | 0.311 |
| Alcohol drinking | 109 (54.8) | 111 (55.8) | 0.879 |
| Family history of cancer | 21 (10.6) | - | |

### *PTGS2* polymorphisms and glioma

We found that the CC+CT genotype of rs5275 was more common in the control group than in the glioma group ($P = 0.033$). In addition, the C allele frequency was higher in the control group than in the glioma group ($P = 0.014$). For rs6681231, although we did not observe a significant difference between the 2 groups in genotype distribution, we found that the C allele frequency was lower in glioma patients than in control subjects ($P = 0.044$). We found no significant difference between these 2 groups for the rs689466 genotype and allele distributions (Table 2).

**Table 2.** Genotype distribution of *PTGS2* SNPNs between cases and controls.

| SNPs | Genotype and allele | Glioma (N = 199) | Control (N = 199) | OR (95%CI) | P value |
|---|---|---|---|---|---|
| rs5275 | CC | 5 (0.025) | 14 (0.070) | | 0.033 |
| | CT | 66 (0.330) | 77 (0.385) | | |
| | TT | 129 (0.645) | 109 (0.545) | | |
| | C | 76 (0.190) | 105 (0.263) | 0.659 [0.471-0.920] | 0.014 |
| | T | 324 (0.810) | 295 (0.738) | | |
| rs689466 | AA | 48 (0.240) | 51 (0.255) | | |
| | AG | 95 (0.475) | 92 (0.460) | | 0.932 |
| | GG | 57 (0.285) | 57 (0.285) | | |
| | A | 191 (0.477) | 194 (0.485) | 0.970 [0.735-1.280] | 0.832 |
| | G | 209 (0.522) | 206 (0.515) | | |
| rs6681231 | CC | 10 (0.050) | 18 (0.090) | | |
| | CG | 28 (0.140) | 32 (0.160) | | 0.221 |
| | GG | 162 (0.810) | 150 (0.750) | | |
| | C | 48 (0.120) | 68 (0.170) | 0.665 [0.446-0.991] | 0.044 |
| | G | 352 (0.880) | 332 (0.830) | | |

As shown in Figure 2, all 3 SNPs are located in 1 haplotype block (|D'| > 0.5) and were available for haplotype analysis ($r^2 < 0.5$). As shown in Table 3, the frequency of the C-A-C haplotype was significantly lower in glioma patients than in control subjects (P = 0.028, OR = 0.628, 95%CI = 0.413-0.955). However, the frequency of the T-A-G haplotype was higher in glioma patients than in control subjects (P = 0.036, OR = 1.418, 95%CI = 1.022-1.967) (Table 3).

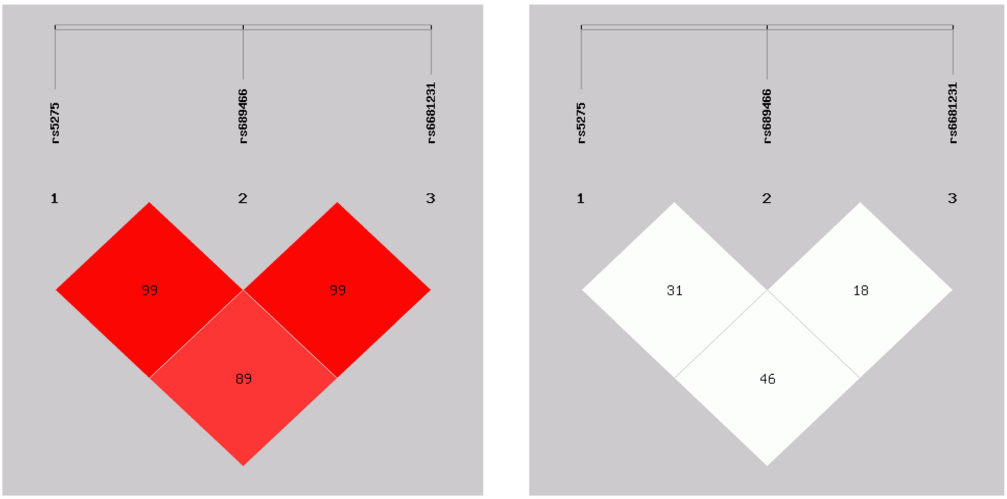


**Figure 2.** Patterns of linkage disequilibrium in the *PTGS2* gene, with their |D'| (**A**) and $r^2$ values (**B**).

**Table 3.** Distribution of haplotypes.

| Haplotype | Glioma | Control | P | OR (95%CI) |
|---|---|---|---|---|
| C-A-C | 41.74 (0.104) | 62.69 (0.157) | 0.028 | 0.628 (0.413-0.955) |
| C-A-G | 34.26 (0.086) | 42.31 (0.106) | 0.338 | 0.794 (0.494-1.275) |
| T-A-G | 108.74 (0.272) | 83.69 (0.209) | 0.036 | 1.418 (1.022-1.967) |
| T-G-G | 208.99 (0.522) | 205.99 (0.515) | 0.802 | 1.036 (0.783-1.371) |

## DISCUSSION

In the present study, we found that *PTGS2* genetic polymorphisms and haplotypes were associated with glioma. This is the first study to reveal the relationship between *PTGS2* genetic polymorphisms and glioma risk in a Chinese population.

COX is a key enzyme involved in the production of prostaglandins from free arachidonic acid; two COX isoforms have been identified (Xie et al., 2011). These isoforms show differences in expression and function. COX-1 is constitutively expressed in most normal tissues, while COX-2 is rarely expressed in normal tissues. COX-1 is thought to be a housekeeping enzyme that is responsible for various physiological functions. However, COX-2 is rapidly induced in response to cytokines, growth factors, and tumor promoters. COX-2-derived prostaglandins participate in immune response suppression, which has been associated with glioma. COX-2 is encoded by the *PTGS2* gene, which is reportedly associated with the risk of various cancers, such as prostate, breast, and bladder cancers.

In the present study, we found that the rs5275 SNP was inversely associated with glioma risk. rs5275 is located in the 3'-untranslated region of the *PTGS2* gene and may influence *PTGS2* RNA half-life. Previous studies suggested that in the proximal upstream region of rs5275, a conserved AU-rich sequence element is present that mediates posttranscriptional degradation of *PTGS2* mRNA. A previous study involving functional analysis to measure *PTGS2* mRNA indicated that a decreased cancer risk was associated with the rs5275 C allele. The mechanism of this function may be related to lower PTGS2 expression.

In this study, we found that the C allele of rs5275 was more common in the control group than in the glioma group, indicating that C allele carriers may have decreased risk of glioma. We also found that rs6681231 was associated with glioma. To further understand the role of these SNPs, we constructed 4 haplotypes using these 3 SNPs. We found that the frequency of the C-A-C haplotype was significantly lower in glioma patients than in control subjects. However, the frequency of the T-A-G haplotype was higher in glioma patients than in control subjects.

In conclusion, the present study suggested that genetic polymorphisms in *PTGS2* were associated with glioma in a Chinese population. The T-A-G haplotype may be a genetic marker for the risk of glioma, but the C-A-C haplotype may act as a protective factor against glioma.

## REFERENCES

Amirian E, Liu Y, Scheurer ME, El-Zein R, et al. (2010). Genetic variants in inflammation pathway genes and asthma in glioma susceptibility. *Neuro-Oncol*. 12: 444-452.

Bhattacharya A, Li Y, Shi Y and Zhang Y (2013). Enhanced inhibition of urinary bladder cancer growth and muscle invasion by allyl isothiocyanate and celecoxib in combination. *Carcinogenesis* 34: 2593-2599.

Chen L, Wang X, Wang H, Li Y, et al. (2012). miR-137 is frequently down-regulated in glioblastoma and is a negative regulator of Cox-2. *Eur. J. Cancer* 48: 3104-3111.

Cheng HB, Xie C, Zhang RY, Hu SS, et al. (2013). *Xeroderma pigmentosum* complementation group f polymorphisms influence risk of glioma. *Asian Pac. J. Cancer Prev.* 14: 4083-4087.

Erdem H, Yildirim U, Uzunlar AK, Cam K, et al. (2013). Relationship among expression of basic-fibroblast growth factor, MTDH/astrocyte elevated gene-1, adenomatous polyposis coli, matrix metalloproteinase 9, and COX-2 markers with prognostic factors in prostate carcinomas. *Niger. J. Clin. Pract*. 16: 418-423.

Goodenberger ML and Jenkins RB (2012). Genetics of adult glioma. *Cancer Genet*. 205: 613-621.

Jankovsky JM, Newkirk KM, Ilha MR and Newman SJ (2013). COX-2 and c-kit expression in canine gliomas. *Vet. Comp. Oncol*. 11: 63-69.

Jhang JF, Jiang YH and Kuo HC (2013). Adding cyclooxygenase-2 inhibitor to alpha blocker for patients with benign prostate hyperplasia and elevated serum prostate specific antigen could not improve prostate biopsy detection rate but improve lower urinary tract symptoms. *Int. J. Clin. Pract*. 67: 1327-1333.

Liu P, Huang Z, Chen Z, Xu R, et al. (2013). Silver nanoparticles: a novel radiation sensitizer for glioma? *Nanoscale* 5: 11829-11836.

Liang HJ, Yan YL, Liu ZM, Chen X, et al. (2013). Association of XRCC3 Thr241Met polymorphisms and gliomas risk: evidence from a meta-analysis. *Asian Pac. J. Cancer Prev*. 14: 4243-4247.

Okada H, Scheurer ME, Sarkar SN and Bondy ML (2013). Integration of epidemiology, immunobiology, and translational research for brain tumors. *Ann. N. Y. Acad. Sci*. 1284: 17-23.

Schebesch KM, Proescholdt M, Höhne J, Hohenberger C, et al. (2013). Sodium fluorescein-guided resection under the YELLOW 560 nm surgical microscope filter in malignant brain tumor surgery - a feasibility study. *Acta Neurochir.* 155: 693-699.

Sivak-Sears NR, Schwartzbaum JA, Miike R, Moghadassi M, et al. (2004). Case-control study of use of nonsteroidal antiinflammatory drugs and glioblastoma multiforme. *Am. J. Epidemiol*. 159: 1131-1139.

Thorat D, Sahu A, Behera R, Lohite K, et al. (2013). Association of osteopontin and cyclooxygenase-2 expression with breast cancer subtypes and their use as potential biomarkers. *Oncol. Lett*. 6: 1559-1564.

Turner MC, Krewski D, Armstrong BK, Chetrit A, et al. (2013). Allergy and brain tumors in the INTERPHONE study:

pooled results from Australia, Canada, France, Israel, and New Zealand. *Cancer Causes Control* 24: 949-960.
Xie X, Ma YT, Fu ZY, Yang YN, et al. (2009). Association of polymorphisms of PTGS2 and CYP8A1 with myocardial infarction. *Clin. Chem. Lab. Med*. 47: 347-352.
Xie X, Ma YT, Yang YN, Fu ZY, et al. (2011). Interaction between COX-2 G-765C and smoking in relation to coronary artery disease in a Chinese Uighur population. *Clin. Chem. Lab. Med*. 49: 55-60.
Zeybek U, Yaylim I, Ozkan NE, Korkmaz G, et al. (2013). Cyclin D1 gene G870A variants and primary brain tumors. *Asian Pac. J. Cancer Prev*. 14: 4101-4106.