Genetic variants in MIR17HG affect the susceptibility and prognosis of glioma in a Chinese Han population

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Abstract

Background: lncRNA MIR17HG was upregulated in glioma, and involved glioma proliferation, migration, invasion and promoted apoptosis. However, the role of MIR17HG polymorphisms on the occurrence and prognosis of glioma is not obvious.

Methods: In the study, 592 glioma patients and 502 control subjects conducted. Agena MassARRAY platform was used to detect the genotype of MIR17HG polymorphisms. Logistic regression analysis was used to evaluate the relation of MIR17HG SNPs to glioma risk by odds ratio (OR) and 95% confidence intervals (CIs). Kaplan-Meier curves, Cox hazards models were performed for assessing the role of these SNPs in glioma prognosis by hazard ratios (HR) and 95% CIs.

Results: We found that rs7318578 (OR = 2.25, p = 3.18x10^{-5}) was significantly associated with glioma susceptibility. Rs17735387 (OR = 1.53, p = 9.05x10^{-3}) and rs7336610 (OR = 1.35, p = 0.016) had a higher glioma susceptibility in the subgroup with age < 40 years. More importantly, rs17735387 (HR = 0.82, log-rank p = 0.026) improved glioma prognosis. GA genotype of rs17735387 had a better overall survival (HR = 0.75, log-rank p = 0.013) and progression free survival (HR = 0.73, log-rank p = 0.032) in patients with I-II glioma.

Conclusion: Our study firstly reported that MIR17HG polymorphisms, especially rs7318578, might be risk factors for glioma susceptibility and rs17735387 improved the prognosis of glioma among Chinese Han population, which might help to enhance the understanding of MIR17HG gene in gliomagenesis.

Background

It is estimated that there would be an 296,851 new cases of brain and central nervous system (CNS) tumor and 241,037 death in 2018, and the incidence and mortality among men are higher than that in women [1]. Glioma is the most frequent neoplasms originated
from neuroglial stem or progenitor cells, accounting for 80% of primary malignant brain cancers with approximately 101,600 individuals diagnosed in China each year [2, 3]. Despite the efforts of diagnosis and therapeutics, the prognosis of glioma is still depressing. Until now, the aetiology of glioma remains unclear. However, environmental and occupational exposures have been identified that related to the occurrence and development of glioma, especially high-dosage ionizing radiation [4]. In addition, genetic factors also have a pivotal contribution to the occurrence and prognosis of glioma. Several association studies have revealed that single nucleotide polymorphisms (SNPs) contribute to glioma risk and survival [5-7].

MIR17HG gene, located on chromosome 13q31.3, is the host gene for the microRNA 17–92 cluster. Functional studies have confirmed that the MIR17HG gene might be involved in cell survival, proliferation, differentiation, and angiogenesis[8]. IncRNA MIR17HG, also as a long noncoding RNA which regulating the expression of miRNA, played the carcinogenic role in various cancers including rectal cancer, gastric cancer, and lung cancer [9-11]. Research has shown that IncRNA MIR17HG was overexpressed in glioma and IncRNA MIR17HG knockdown inhibited glioma proliferation, migration, and invasion, suggesting IncRNA MIR17HG might facilitate glioma malignant progress [12]. Recent increasing evidence has indicated that the genetic polymorphisms of MIR17HG was associated with the occurrence of multiple tumors, such as lymphoma, colorectal cancer, breast cancer [13-15]. However, the role of MIR17HG variants on glioma occurrence and prognosis is not obvious.

Here, we analyzed the association of selected MIR17HG SNPs and glioma susceptibility among the Chinese Han population, and examined the possible role of these polymorphisms in different glioma subgroups stratified by age, gender and grade. We also evaluated the influence of MIR17HG genetic variants on the survival of glioma patients.
Materials And Methods

Subjects

There were 592 glioma patients and 502 control subjects conducted in this study. All participants were genetically unrelated Chinese Han population for at least three generations. Glioma patients who newly diagnosed and confirmed by histopathology were enrolled from the department of Neurosurgery at the Second Affiliated Hospital of Hainan Medical University. Patients who had cancer history and other systemic or complex diseases were excluded. Age- and gender-matched healthy controls were recruited from physical examination center of the hospital. The controls were free from any cancer and brain and central nervous system related disease. Standardized questionnaires and medical records were used to gather demographic and clinical information. The follow-up information was obtained by telephone and return visit, and the survival time, progress and outcome were recorded. After, approximately 5 mL blood sample was collected for further analysis. Our research was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University and was in the Declaration of Helsinki. Written informed consent was obtained from each participant.

Genotyping

Genomic DNA was purified by a commercially available GoldMag DNA Purification Kit (GoldMag Co. Ltd, Xi’an City, China). NanoDrop 2000 (Thermo Scientific, Waltham, MA, USA) was used for checking the DNA quality. Five MIR17HG SNPs (rs17735387, rs72640334, rs7318578, rs7336610, and rs75267932) were identified via the NCBI dbSNP database, the 1000 Genomes Project data with minor allele frequencies (MAFs) > 5% among Chinese Beijing Han population and Haploview software based on a pairwise linkage disequilibrium ($r^2 > 0.80$). MIR17HG polymorphisms were genotyped using Agena
MassARRAY platform (Agena, San Diego, CA, U.S.A.) as previously described[16]. Primers sequences were presented in Supplementary Table 1. Genotyping was in a blinded manner and the call rate ≥ 0.99. For quality control, 10% blind and random samples were repeated genotyping, with a 100% reproducibility.

Data Analysis

SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and PLINK 2.1.7 package were used for statistical analyses. The Chi square test or Student’s t-test was conducted to compare the differences between patients and controls in age and gender distributions, as appropriate. Hardy–Weinberg equilibrium (HWE) was examined for the controls using goodness-of-fit $\chi^2$ test. Logistic regression analysis was used to analyze the genetic effects of MIR17HG SNPs on glioma risk by calculating odds ratio (OR) and 95% confidence intervals (CIs) with adjustment for age and sex. The overall survival (OS) and progression-free survival (PFS) of glioma patients were plotted by Kaplan–Meier survival curves. Univariate and multivariate Cox proportional hazards models were performed for assessing the role of MIR17HG polymorphisms in glioma prognosis by calculating hazard ratio (HR) and 95% CIs. A two-tailed $p$ value of < 0.05 was statistically significant, whereas a value of corrected $p$ < 0.05/(5⋅4) was considered significant after multiple correction.

Results

Participants’ features

The features of patients and controls were presented in Table 1. The case group consisted of 592 patients with glioma (40.53 ± 13.90 years, 55.1% males) and 502 healthy controls (40.46 ± 18.08 years, 54.8% males). The distribution of age ($p = 0.934$) and sex ($p = 0.924$) was no statistically differences. Among the cases, 378 patients were WHO grade I + II, and 214 were grade III + IV.
### Table 1
Characteristics of patients with glioma and health controls

| Characteristics               | Cases (n = 592) | Controls (n = 502) | p     |
|------------------------------|----------------|-------------------|-------|
| Age (Mean ± SD, years)       | 40.53 ± 13.90  | 40.46 ± 18.08     | 0.934 |
| Gender (Males/Females)       | 326/266        | 275/227           |       |
| WHO grade                    |                |                   |       |
| I                            | 43             |                   |       |
| II                           | 335            |                   |       |
| III                          | 149            |                   |       |
| IV                           | 65             |                   |       |
| Surgical method              |                |                   |       |
| STR                          | 177            |                   |       |
| NTR                          | 8              |                   |       |
| GTR                          | 407            |                   |       |
| Radiotherapy                 |                |                   |       |
| No                           | 58             |                   |       |
| Conformal radiotherapy       | 159            |                   |       |
| Gamma knife                  | 375            |                   |       |
| Chemotherapy                 |                |                   |       |
| No                           | 349            |                   |       |
| Yes                          | 243            |                   |       |
| Survival condition           |                |                   |       |
| Survival                     | 41             |                   |       |
| Lost                         | 24             |                   |       |
| Death                        | 527            |                   |       |

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

The genotyping results of MIR17HG variants

Five SNPs in MIR17HG were genotyped to determine the possible effect of MIR17HG variants on glioma risk or prognosis. Minor allele frequencies in patients and controls were displayed in Supplementary Table 2. All genotype frequencies of studied variants among controls were in HWE (p > 0.05), and the genotyping rate exceeded 99.5%.

### The correlation between MIR17HG variants and glioma risk

The genotype frequencies and allele frequencies of these SNPs in MIR17HG were displayed in Table 2. The frequencies of C allele (34.9% vs 28.9%) and CC genotype (19.7% vs 9.0%) of rs7318578 were higher in glioma patients compared the controls. In details, rs7318578 C allele (OR = 1.32, 95% CI: 1.10–1.58, p = 2.63·10^{-3}) and CC genotype (OR = 2.25, 95% CI: 1.54–3.31, p = 3.18·10^{-5}) were related to increased glioma susceptibility compared with the A allele and AA genotype, respectively. After applying the of Bonferroni correction (threshold p = 0.0025), rs7318578 CC genotype was still found to be significant.
for glioma risk. Moreover, rs7318578 variant showed a 1.26-fold increased glioma occurrence under the additive model (OR = 1.26, 95% CI: 1.07–1.49, p = 6.23·10^{-3}). There was no association between other SNPs and glioma risk.

We further explored the glioma risk related to MIR17HG SNPs by stratifying for age, sex and WHO grade. Among the subjects of age ≥ 40 years, carriers of the rs7318578 CC genotype showed a 2.46-fold increased glioma risk compared with individuals carrying the AA genotype (OR = 2.46, 95% CI: 1.42–4.28, p = 1.41·10^{-3}, Table 3). The significance still existed after Bonferroni correction. Additionally, rs17735387 was a risk factor for glioma

## Table 2
The effect of MIR17HG variants on the risk of glioma

| SNP ID    | Allele/Genotype | Control | Case       | OR (95%CI)     | p       |
|-----------|-----------------|---------|------------|----------------|---------|
| rs17735387| G               | 829     | 964        | 1              | 1       |
|           | A               | 175     | 220        | 1.08 (0.87-1.35)| 0.486   |
|           | GG              | 341     | 395        | 1              | 1       |
|           | GA              | 147     | 174        | 1.02 (0.79-1.33)| 0.871   |
|           | AA              | 14      | 23         | 1.42 (0.72-2.80)| 0.315   |
|           | GA + AA         | 161     | 197        | 1.06 (0.82-1.36)| 0.672   |
|           | GG + GA + AA    | /       | /          | 1.08 (0.87-1.34)| 0.488   |
| rs72640334| C               | 916     | 1070       | 1              | 1       |
|           | A               | 86      | 110        | 1.10 (0.81-1.47)| 0.547   |
|           | CC              | 418     | 487        | 1              | 1       |
|           | CA              | 80      | 96         | 1.03 (0.74-1.43)| 0.860   |
|           | AA              | 3       | 7          | 2.01 (0.51-7.83)| 0.316   |
|           | CA + AA         | 83      | 103        | 1.07 (0.78-1.46)| 0.696   |
|           | CC + CA + AA    | /       | /          | 1.09 (0.82-1.47)| 0.550   |
| rs7318578 | A               | 714     | 768        | 1              | 1       |
|           | C               | 290     | 412        | 1.32 (1.10-1.58)| 2.63·10^{-3}|
|           | AA              | 257     | 294        | 1              | 1       |
|           | AC              | 200     | 180        | 0.79 (0.61-1.02)| 0.073   |
|           | CC              | 45      | 116        | 2.25 (1.54-3.31)| 3.18·10^{-5}*|
|           | AC + CC         | 245     | 296        | 1.06 (0.83-1.34)| 0.654   |
|           | AA + AC + CC    | /       | /          | 1.26 (1.07-1.49)| 6.23·10^{-3}|
| rs7336610 | T               | 537     | 602        | 1              | 1       |
|           | C               | 475     | 580        | 1.07 (0.90-1.27)| 0.438   |
|           | TT              | 141     | 144        | 1              | 1       |
|           | TC              | 245     | 314        | 1.26 (0.94-1.67)| 0.119   |
|           | CC              | 115     | 133        | 1.13 (0.80-1.59)| 0.477   |
|           | TC + CC         | 360     | 447        | 1.22 (0.93-1.59)| 0.157   |
|           | TT + TC + CC    | /       | /          | 1.07 (0.9-1.27)| 0.433   |
| rs75267932| A               | 879     | 1061       | 1              | 1       |
|           | G               | 125     | 123        | 0.82 (0.63-1.06)| 0.130   |
|           | AA              | 385     | 479        | 1              | 1       |
|           | AG              | 109     | 103        | 0.76 (0.56-1.03)| 0.073   |
|           | GG              | 8       | 10         | 1.01 (0.39-2.58)| 0.988   |
|           | AG + GG         | 117     | 113        | 0.78 (0.58-1.04)| 0.089   |
|           | AA + AG + GG    | /       | /          | 0.82 (0.63-1.07)| 0.138   |

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. p values were calculated by logistic regression analysis with adjustments for age and gender. Bold p < 0.05 means the data is statistically significant. * After Bonferroni correction (p < 0.05/(5×4)) means the data is statistically significant.
occurrence: A vs G: OR = 1.53, 95% CI: 1.11–2.11, p = 9.05⋅10^{-3}; AA vs GG: OR = 3.27, 95% CI: 1.09–9.80, p = 0.034; GA + AA vs GG: OR = 1.57, 95% CI: 1.07–2.30, p = 0.021; GG + GA + AA: OR = 1.56, 95% CI: 1.12–2.18, p = 8.55⋅10^{-3} at age < 40 years. MIR17HG rs7318578 C allele (OR = 1.37, 95% CI: 1.05–1.79, p = 0.020) and CC genotype (OR = 1.88, 95% CI: 1.08–3.28, p = 0.026) conferred the increased risk to develop glioma in subjects aged younger 40 years. Results of multiple model showed that rs7336610 conferred to the high glioma susceptibility at age < 40 years (C vs T: OR = 1.35, 95% CI: 1.06–1.73, p = 0.016; TC vs TT: OR = 1.56, 95% CI: 1.02–2.39, p = 0.041; CC vs TT: OR = 1.72, 95% CI: 1.02–2.92, p = 0.044; TC + CC vs TT: OR = 1.61, 95% CI: 1.07–2.41, p = 0.022; TT + TC + CC: OR = 1.33, 95% CI: 1.02–1.73, p = 0.034).
Table 3
The effect of MIR17HG variants on the risk of glioma stratified by age and gender

| SNP ID  | Allele/Genotype | OR (95%CI) | p     | OR (95%CI) | p     |
|---------|-----------------|------------|-------|------------|-------|
|         | Age (year)      | ≥ 40       | < 40  |            |       |
| rs17735387 | G               | 0.79 (0.59-1.07) | 0.128 | 1.53 (1.11-2.11) | 9.05⋅10⁻³ |
|         | A               |            |       | 1.05 (0.83-1.32) | 0.621 |
|         | GG              |            |       | 1.02 (0.81-1.28) | 0.858 |
|         | GA              |            |       | 0.94 (0.73-1.22) | 0.581 |
|         | AA              |            |       | 0.82 (0.65-1.03) | 0.085 |
|         | GA + AA         |            |       | 0.82 (0.65-1.03) | 0.085 |
|         | GG + GA + AA    |            |       | 0.80 (0.63-1.01) | 0.043 |
| rs7318578 | A               | 1.27 (0.99-1.62) | 0.063 | 1.37 (1.05-1.79) | 0.020 |
|         | C               |            |       | 1.18 (0.89-1.56) | 0.397 |
|         | AA              |            |       | 1.18 (0.89-1.56) | 0.397 |
|         | AC              |            |       | 0.92 (0.70-1.21) | 0.545 |
|         | CC              |            |       | 0.94 (0.72-1.22) | 0.727 |
|         | AC + CC         |            |       | 0.92 (0.70-1.21) | 0.545 |
|         | AA + AC + CC    |            |       | 1.22 (0.97-1.54) | 0.076 |
| rs7336610 | T               | 1.17 (0.93-1.48) | 0.184 | 1.35 (1.06-1.73) | 0.016 |
|         | C               |            |       | 1.21 (0.97-1.51) | 0.100 |
|         | TT              |            |       | 1.21 (0.97-1.51) | 0.100 |
|         | TC              |            |       | 1.35 (1.09-1.68) | 0.003 |
|         | CC              |            |       | 1.42 (1.15-1.75) | 0.001 |
|         | TC + CC         |            |       | 1.35 (1.09-1.68) | 0.003 |
|         | TT + TC + CC    |            |       | 1.16 (0.92-1.45) | 0.213 |
| Gender  | Male            |            |       | 0.84 (0.65-1.09) | 0.165 |
|         | Female          |            |       | 0.84 (0.65-1.09) | 0.165 |
| rs7318578 | A               | 1.18 (0.93-1.50) | 0.183 | 1.53 (1.16-2.01) | 2.49⋅10⁻³ |
|         | AA              |            |       | 1.18 (0.93-1.50) | 0.183 |
|         | AC              |            |       | 0.70 (0.49-1.05) | 0.532 |
|         | CC              |            |       | 0.90 (0.61-1.33) | 0.606 |
|         | AC + CC         |            |       | 0.90 (0.61-1.33) | 0.606 |
|         | AA + AC + CC    |            |       | 1.15 (0.92-1.43) | 0.226 |

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

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

Bold p < 0.05 means the data is statistically significant.

* After Bonferroni correction [(p < 0.05)/(5⋅4)] means the data is statistically significant.

Stratified by gender (Table 3), the significant associations between rs7318578 polymorphism and glioma risk were observed in males (CC vs AA: OR = 1.80, 95% CI: 1.10-2.95, p = 0.020) and females (CC vs AA: OR = 3.08, 95% CI: 1.67-5.67, p = 3.19⋅10⁻⁴ and AA + AC + CC: OR = 1.43, 95% CI: 1.11-1.84, p = 5.96⋅10⁻³). Especially, the association of allele model of rs7318578 in females was still significant after multiple comparisons (C vs A: OR = 1.53, 95% CI: 1.16-2.01, p = 2.49⋅10⁻³).

In stratified analyses with WHO grade, rs7336610 showed genotype difference between patients with III-IV and patients with I-II, with OR from 1.31 to 1.72 (TC vs TT: OR = 1.58, 9.56⋅10⁻³).
95% CI: 1.02–2.43, p = 0.039; CC vs TT: OR = 1.72, 95% CI: 1.04–2.86, p = 0.036; TC + CC vs TT: OR = 1.62, 95% CI: 1.07–2.45, p = 0.022; and TT + TC + CC: OR = 1.31, 95% CI: 1.02–1.68, p = 0.035), as shown in Table 4.

Table 4
The effect of MIR17HG variants on WHO grade of glioma

| SNP ID     | Allele/Genotype | I-II | III-IV | OR (95% CI)      | p   |
|------------|-----------------|------|--------|-----------------|-----|
| rs7336610  | T               | 400  | 202    | 1.26 (1.00–1.60) | 0.053 |
|            | C               | 354  | 226    | 1.58 (1.02–2.43) | 0.039 |
|            | TT              | 103  | 41     | 1.72 (1.04–2.86) | 0.036 |
|            | TC              | 194  | 120    | 1.62 (1.07–2.45) | 0.022 |
|            | TC + CC         | 274  | 173    | 1.31 (1.02–1.68) | 0.035 |
|            | TT + TC + CC    | /    | /      |                  |     |

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval. p values were calculated by logistic regression analysis with adjustments for age and gender. Bold p < 0.05 means the data is statistically significant.

The correlation between MIR17HG variants and glioma prognosis

Next, we investigated the correlation between MIR17HG variants and PFS or OS of glioma by Kaplan–Meier survival method, univariate and multivariate Cox proportional hazard model. Rs17735387 was related to PFS of glioma (Log-rank p = 0.026), as shown in Fig. 1 and Table 5. Multivariate Cox proportional hazard mode adjusted for age, sex WHO grade, surgical method, use of radiotherapy and chemotherapy showed that carriers of rs17735387 GA genotype presented longer PFS than GG patients (HR = 0.82, 95% CI: 0.68–0.99, p = 0.042; Table 6). No statistically significant associations were found between other MIR17HG polymorphisms and glioma prognosis.
| SNP ID  | Genotype | OS | PFS |
|---------|----------|----|-----|
|         |          | Event/Total | SR (1/-3-year) | MST (month) | Log-rank p | Event/Total | SR (1/-3-year) | MST (month) | Log-rank p |
| rs177353 | GG       | 356/395     | 0.299/0.0 82  | 11.0        | 0.070      | 355/394     | 0.157/0.0 88  | 8.0          | 0.026      |
|         | GA       | 153/174     | 0.360/0.1 01  | 12.0        |            | 150/170     | 0.216/0.0 94  | 8.0          |            |
|         | AA       | 18/23       | 0.435/-     | 12.0        |            | 18/23       | 0.304/-     | 9.0          |            |
| rs726403 | CC       | 433/487     | 0.319/0.0 92  | 11.0        | 0.365      | 430/483     | 0.179/0.0 92  | 8.0          | 0.470      |
|         | CA       | 86/96       | 0.333/0.0 82  | 10.0        |            | 85/95       | 0.179/0.0 93  | 8.0          |            |
|         | AA       | 7/7         | 0.143/-     | 10.0        |            | 7/7         | 0.286/-     | 8.0          |            |
| rs731857 | AA       | 263/294     | 0.335/0.0 85  | 12.0        | 0.755      | 262/293     | 0.192/0.0 83  | 8.0          | 0.527      |
|         | AC       | 160/180     | 0.306/0.0 93  | 11.0        |            | 159/178     | 0.163/0.0 97  | 8.0          |            |
|         | CC       | 102/116     | 0.319/0.1 11  | 11.0        |            | 101/115     | 0.316/-     | 8.0          |            |
| rs733661 | TT       | 129/144     | 0.326/0.0 95  | 11.0        | 0.740      | 129/144     | 0.174/0.0 96  | 8.0          | 0.516      |
|         | TC       | 281/314     | 0.296/0.0 85  | 11.0        |            | 279/312     | 0.167/0.0 89  | 8.0          |            |
|         | CC       | 116/133     | 0.381/0.0 95  | 12.0        |            | 114/130     | 0.221/0.0 98  | 8.0          |            |
| rs752679 | AA       | 425/479     | 0.323/0.0 91  | 11.0        | 0.766      | 422/475     | 0.185/0.0 92  | 8.0          | 0.634      |
|         | AG       | 92/103      | 0.311/0.0 95  | 10.0        |            | 91/102      | 0.176/0.0 97  | 8.0          |            |
|         | GG       | 10/10       | 0.400/-     | 12.0        |            | 10/10       | 0.100/-     | 8.0          |            |
| Low-grade glioma (I-II) | | | | | |
| rs177353 | GG       | 232/260     | 0.292/0.0 90  | 11.0        | 0.032      | 232/260     | 0.158/0.0 93  | 8.0          | 0.013      |
|         | GA       | 86/102      | 0.398/0.1 49  | 12.0        |            | 84/100      | 0.255/0.1 35  | 9.0          |            |
|         | AA       | 12/16       | 0.500/-     | 12.0        |            | 12/16       | 0.375/-     | 9.0          |            |

Abbreviations: OS: Overall survival; PFS: Progression free survival; SR: Survival rate, MST, median survival time. Log-rank p values were calculated using the Chi-Square test. Bold p < 0.05 indicates statistical significance.
Table 6
Cox proportional hazards model of the association between MIR17HG variants and OS and PFS of glioma patients

| SNP ID | Genotype | Univariate | Multivariate a |
|--------|----------|------------|----------------|
|        |          | OS         | PFS            | OS             | PFS             |
|        |          | HR (95% CI) | p              | HR (95% CI)    | p              | HR (95% CI)    | p              |
| rs177353 | GG       | 0.85 (0.70–1.03) | 0.097 | 0.83 (0.69–1.01) | 0.059 | 0.84 (0.69–1.01) | 0.067 | 0.82 (0.68–0.99) | 0.042 |
| rs177353 | GA       | 0.70 (0.43–1.12) | 0.136 | 0.66 (0.41–1.07) | 0.089 | 0.84 (0.46–1.19) | 0.211 | 0.71 (0.44–1.14) | 0.158 |
| rs177353 | AA       | 1.08 (0.86–1.36) | 0.508 | 1.07 (0.85–1.35) | 0.560 | 1.08 (0.85–1.37) | 0.520 | 1.09 (0.86–1.38) | 0.467 |
| rs726403 | CC       | 1.56 (0.74–3.29) | 0.247 | 1.44 (0.68–3.05) | 0.335 | 1.25 (0.58–2.66) | 0.569 | 1.20 (0.56–2.56) | 0.633 |
| rs731857 | AA       | 1.07 (0.88–1.30) | 0.493 | 1.11 (0.91–1.35) | 0.310 | 1.07 (0.88–1.30) | 0.516 | 1.10 (0.90–1.34) | 0.353 |
| rs731857 | AC       | 1.03 (0.82–1.30) | 0.776 | 1.04 (0.82–1.30) | 0.762 | 1.05 (0.83–1.32) | 0.701 | 1.04 (0.83–1.31) | 0.725 |
| rs733661 | TT       | 1.00 (0.80–1.23) | 0.98  | 0.99 (0.81–1.23) | 0.957 | 0.96 (0.78–1.18) | 0.703 | 0.96 (0.78–1.18) | 0.698 |
| rs752679 | CC       | 0.93 (0.72–1.19) | 0.549 | 0.89 (0.69–1.15) | 0.381 | 0.91 (0.71–1.17) | 0.480 | 0.89 (0.69–1.15) | 0.375 |
| rs177353 | AA       | 1.07 (0.85–1.33) | 0.585 | 1.07 (0.85–1.34) | 0.568 | 1.04 (0.83–1.31) | 0.727 | 1.05 (0.84–1.32) | 0.671 |
| rs177353 | GG       | 1.14 (0.61–2.14) | 0.675 | 1.24 (0.66–2.32) | 0.502 | 1.17 (0.62–2.20) | 0.633 | 1.24 (0.66–2.34) | 0.502 |

Low-grade glioma (Ⅰ-Ⅱ)

| SNP ID | Genotype | Univariate | Multivariate a |
|--------|----------|------------|----------------|
|        |          | OS         | PFS            | OS             | PFS             |
|        |          | HR (95% CI) | p              | HR (95% CI)    | p              | HR (95% CI)    | p              |
| rs177353 | GG       | 0.77 (0.60–0.99) | 0.042 | 0.75 (0.58–0.97) | 0.024 | 0.75 (0.58–0.96) | 0.024 | 0.73 (0.57–0.91) | 0.016 |
| rs177353 | AA       | 0.64 (0.36–1.15) | 0.138 | 0.62 (0.35–1.11) | 0.110 | 0.68 (0.38–1.22) | 0.195 | 0.70 (0.39–1.26) | 0.233 |

Abbreviations: OS: Overall survival; PFS: Progression free survival; HR: Hazard ratio; CI: Confidence interval.

a p values were calculated by Cox multivariate analysis with adjustments for gender, age, WHO grade, surgical method, use of radiotherapy and chemotherapy.

Bold p < 0.05 indicates statistical significance.

In patients with low-grade glioma (Ⅰ-Ⅱ), Kaplan–Meier method revealed the association between MIR17HG rs17735387 and PFS (Log-rank p = 0.013) or OS (Log-rank p = 0.032) (Fig. 2). Univariate Cox proportional hazard model presented that GA genotype of rs17735387 had a better OS (HR = 0.77, 95% CI: 0.60–0.99, p = 0.042) and PFS (HR = 0.75, 95% CI: 0.58–0.97, p = 0.024) when compared to GG genotype in patients with Ⅰ-Ⅱ glioma.
Moreover, multivariate Cox proportional hazard model also display that improved prognosis for glioma was also seen for rs17735387-GA genotype (OS: HR = 0.75, 95% CI: 0.58-0.96, p = 0.024 and PFS: HR = 0.73, 95% CI: 0.57-0.94, p = 0.016).

Discussion

The present study explored the possible correlation between MIR17HG variants and the occurrence and prognosis of glioma in a Chinese Han population. Our data revealed that rs7318578, rs17735387 and rs7336610 polymorphisms statistically conferred to the increased susceptibility to glioma. We also found that rs17735387 was related to a better prognosis of glioma patients. To our knowledge, we firstly reported that MIR17HG polymorphisms might contribute to glioma susceptibility and patients’ survival. MIR17HG gene also called c13orf25 and Oncomir-1, encoding a polycistronic miR-17-92 cluster encompassed six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1). The miR-17-92 cluster was deregulated in glioma, pointing to a key role of these miRNA in gliomagenesis [17, 18]. Schulte JH et al. reported miR-17-92 cluster amplification in neuroblastomas, which associated with poor prognosis [19]. It has been reported that IncRNA MIR17HG was upregulated in glioma tissues and cell lines and acted as ceRNA to sponge miR-346/miR-425-5p in regulating glioma malignant [12]. Yuze Cao et al. reported that IncRNA MIR17HG-mediated ceRNA network was identified to be potential prognostic biomarkers in glioblastoma [20]. Moreover, Xue Leng et al. observed that MIR17HG had higher expression in glioma and involved in piR-DQ590027/ IncRNA MIR17HG/miR-153(miR-377)/FOXR2 pathway which involved in regulating the permeability of glioma-conditioned normal blood-brain barrier [21]. These results suggested that IncRNA MIR17HG could be of pathogenic importance in the development and prognosis of glioma. Several previous studies have reported the effect of MIR17HG genetic polymorphisms on the susceptibility to various disease including tumors [22, 23], but not
in glioma.

Considering the importance of MIR17HG in the carcinogenic process of glioma, we hypothesized that MIR17HG polymorphisms might also contribute to glioma development. Here, we explored the association of five SNPs in MIR17HG with glioma risk and prognosis in a Chinese Han population. We found that rs7318578 contributed to glioma susceptibility and especially the significance still existed after Bonferroni correction. The incidence rates of glioma, that is, the rate of newly diagnosed tumor, are with increasing age and male gender[24]. We further analyzed whether the genotypic effects on MIR17HG risk were dependent on age and sex. After Bonferroni correction, rs7318578 conferred to increase the occurrence of glioma at age ≥ 40 years or in females. In addition, rs17735387 and rs7336610 also had a higher glioma susceptibility in the subgroup with age < 40 years. These indicated that the effect of MIR17HG polymorphisms on glioma occurrence presented age and sex difference. More importantly, we found that rs17735387 was related to the improved prognosis of glioma patients, particularly in low-grade glioma. Previously, rs7336610 was reported to be related to the risk of multiple myeloma and breast cancer, and rs17735387 not share any relationship with multiple myeloma risk and prognosis [14, 22]. These results suggested that MIR17HG polymorphisms might have a different effect on the occurrence of different cancer types. However, our findings need further studies to confirm.

Inevitably, some limitations should not be ignore. First, all individuals including glioma patients and healthy controls were from the same hospital, therefore the selection bias cannot be ruled out. Second, due to some deficient data about environmental exposure and dietary, the interaction between environment and genetics was needed to address in larger prospective studies. Third, the effect of these SNPs on miR-17-92 cluster or lncRNA MIR17HG was not assessed.
Conclusion

In conclusion, we reported that MIR17HG polymorphisms, especially rs7318578, might be risk factors for glioma susceptibility and rs17735387 variant improved the prognosis of glioma among Chinese Han population. Our study firstly provided evidence about the effect of MIR17HG polymorphisms on glioma risk and prognosis, which might help to enhance the understanding of MIR17HG gene in gliomagenesis. Further studies are required to validate our findings and to elucidate the function of these MIR17HG SNPs in glioma.

Abbreviations

SNP, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence intervals; HR, hazard ratios; OS, overall survival; PFS, progression-free survival; MAFs, minor allele frequencies; HWE, hardy-weinberg equilibrium.

Declarations

Ethics approval and consent to participate

Our research was approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University and was in the Declaration of Helsinki. Written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Availability of data and material

All the data regarding the findings are available within the manuscript. Anyone who is interested in the information should contact the corresponding author.

Competing interests

The authors declare that they have no conflict of interest.
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No.

Authors' contributions

The work presented here was carried out in collaboration between all authors. Jigao Feng and Yibin Ouyang carried out the molecular genetic studies and drafted the manuscript. Dedong Xu designed the methods and experiments, performed the statistical analyses and interpreted the results. Qinglong He and Dayuan Liu designed primers and performed the SNP genotyping experiments. Xudong Fan and Pengxiang Xu collected clinical information about patients and performed the SNP genotyping experiments. Yehe Mo conceived of the study, worked on associated data collection and their interpretation, participated in the design and coordination of the study, and funded the study. All authors read and approved the final manuscript.

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Figures

![Graph showing the effect of MIR17HG rs17735387 on the survival of overall glioma patients.](image)

**Figure 1**

Effect of MIR17HG rs17735387 on the survival of overall glioma patients.
Figure 2

Effect of MIR17HG rs17735387 on the survival of patients with low-grade glioma.

The survival curve for overall survival (a) and progression free survival (b).

Supplementary Files
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