Original Article

Association between regulator of telomere elongation helicase 1 polymorphism and susceptibility to glioma

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Abstract: Background: Glioma is the most devastating type of malignant brain tumors in adults. Genetic factors play important roles in the pathogenesis of glioma. In recent years, some studies found that there were significant association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma susceptibility, however, the results were controversial. The aim of this study was to obtain a more exact estimation of the association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma through a meta-analysis. Methods: The meta-analysis included 19 published case-control studies involving 8541 cases and 14226 controls. The included papers were searched from PubMed and Embase database. Odds ratio (OR) with 95% confidence interval (95% CI) were used to evaluate the association of regulator of telomere elongation helicase 1 rs6010620 polymorphism with glioma. Results: A significant association between regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma susceptibility was observed for GG vs. AA+AG (OR=1.28, 95% CI=1.14-1.43) and G vs. A (OR=1.07, 95% CI=1.03-1.10). Further subgroup analysis based on ethnicity showed similar results in Asians and Caucasians. In the subgroup analysis of source of control, a significant association between the G allele and glioma susceptibility were found in population-based group and hospital-based group. Conclusions: The meta-analysis suggested that regulator of telomere elongation helicase 1 rs6010620 polymorphism was a risk factor for glioma. And this study also suggested that rs6010620 GG genotype and G allele may be indicators for the risk of glioma.

Keywords: Regulator of telomere elongation helicase 1, glioma, polymorphism, susceptibility

Introduction

Glioma, the most common type of brain tumors in adults, arises from glial cells and starts in the brain or spine, which accounts for about 30% of all tumors in central nervous system and 80% of malignant tumors in brain [1]. The pathogenesis of glioma involves various factors including pollution, living environment, electromagnetic radiation (cells phones), infection and genetic factor. Among the factors, genetic factors play an important role in the pathogenesis of glioma [2, 3].

Regulator of telomere elongation helicase 1 gene, located in 20q13.3, plays an important role in DNA repair, ATP-dependent DNA helicase activity, acid binding, and apoptosis [4, 5]. Previous researches have suggested that RTELI contributes to genomic stability, DNA replication and telomere maintenance [4, 6]. Moreover, the inactivation of regulator of telomere elongation helicase 1 could cause chromosome breaks, fusions and telomere loss [7]. In addition, the increasing studies have showed that there exists significant association between regulator of telomere elongation helicase 1 polymorphisms and glioma susceptibility.

Among the polymorphisms, regulator of telomere elongation helicase 1 rs6010620 is the most studied single nucleotide polymorphism (SNP). However, the relationship of regulator of telomere elongation helicase 1 rs6010620 and glioma was still inconclusive. One meta-analysis conducted by Zhao et al., have suggested that regulator of telomere elongation helicase 1 rs6010620 is associated with the increased risk for glioma under four genetic models [8]. While, Li et al. have reported that the GG geno-
type of rs6010620 acts as the protective genotype for glioma [9]. Therefore, we conducted a meta-analysis with 8541 cases and 14226 controls to derive a more precise estimation of the correlation between regulator of telomere elongation helicase 1 rs6010620 and glioma risk.

Materials and methods

Search strategy and inclusion criteria

We searched in PubMed and Embase databases with the following key words “regulator of telomere elongation helicase 1”, “RTEL1”, “polymorphism” and “glioma”.

Inclusion criteria were defined as follows: (1) case-control studies estimating the relationship of regulator of telomere elongation helicase 1 rs6010620 with glioma risk; (2) sufficient data for evaluating the odds ratio (OR) with 95% CI; (3) data collection and analysis must be statistically acceptable. If the studies with overlapping data published by the same investigators, we included the most recent or complete study.

Data extraction

The data were extracted by two investigators according to the inclusion criteria. For controversial evaluation, the investigators should discuss with other members of the team until a consensus was reached.

The data extracted from the articles included the name of first author, publication date, ethnicity, country of origin, number of cases and controls, genotyping method, genotype frequencies in cases and controls and source of the control and Hardy-Weinberg equilibrium (HWE).

Statistical analysis

Pooled ORs with 95% CIs were conducted to assess the strength of the association between regulator of telomere elongation helicase 1 rs6010620 and glioma risk.
## Table 1. Principle characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Control source</th>
<th>Genotyping method</th>
<th>Sample size</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Sample size</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shete (England)</td>
<td>2009</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR/MALDI-TOF-MS</td>
<td>631</td>
<td>1031</td>
<td>1.06 (1.02, 1.10)</td>
<td>0.775</td>
<td>697</td>
<td>0.69</td>
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<tr>
<td>Shete (America)</td>
<td>2009</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR/MALDI-TOF-MS</td>
<td>1247</td>
<td>1997</td>
<td>1.07 (1.00, 1.15)</td>
<td>462</td>
<td>2009</td>
<td>0.09</td>
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<tr>
<td>Shete (France)</td>
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<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR/MALDI-TOF-MS</td>
<td>1332</td>
<td>2210</td>
<td>1.10 (0.99, 1.22)</td>
<td>264</td>
<td>2009</td>
<td>0.18</td>
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<tr>
<td>Shete (Germany)</td>
<td>2009</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR/MALDI-TOF-MS</td>
<td>499</td>
<td>819</td>
<td>1.12 (1.05, 1.19)</td>
<td>37</td>
<td>2009</td>
<td>0.000</td>
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<tr>
<td>Shete (Sweden)</td>
<td>2009</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR/MALDI-TOF-MS</td>
<td>645</td>
<td>1055</td>
<td>1.04 (0.98, 1.10)</td>
<td>200</td>
<td>2009</td>
<td>0.10</td>
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<tr>
<td>Schoemaker (Denmark)</td>
<td>2010</td>
<td>England</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>122</td>
<td>204</td>
<td>1.04 (0.98, 1.10)</td>
<td>0.10</td>
<td>454</td>
<td>1.03 (0.99, 1.08)</td>
</tr>
<tr>
<td>Schoemaker (Finland)</td>
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<td>England</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>95</td>
<td>160</td>
<td>1.07 (0.99, 1.16)</td>
<td>30</td>
<td>2010</td>
<td>0.05</td>
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<tr>
<td>Schoemaker (Sweden)</td>
<td>2010</td>
<td>England</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>200</td>
<td>340</td>
<td>1.07 (0.99, 1.16)</td>
<td>30</td>
<td>2010</td>
<td>0.05</td>
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<td>Schoemaker (UK-North)</td>
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<td>England</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>376</td>
<td>610</td>
<td>1.04 (0.98, 1.10)</td>
<td>44</td>
<td>2010</td>
<td>0.05</td>
</tr>
<tr>
<td>Schoemaker (UK-South)</td>
<td>2010</td>
<td>England</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
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<td>383</td>
<td>1.04 (0.98, 1.10)</td>
<td>28</td>
<td>2010</td>
<td>0.05</td>
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<tr>
<td>Chen</td>
<td>2011</td>
<td>China</td>
<td>Asian</td>
<td>HBI</td>
<td>MassARRAY</td>
<td>958</td>
<td>640</td>
<td>1.03 (0.99, 1.08)</td>
<td>277</td>
<td>1.03 (0.99, 1.08)</td>
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<tr>
<td>Wang</td>
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<td>Caucasian</td>
<td>Mixed</td>
<td>HumanHap</td>
<td>332</td>
<td>535</td>
<td>1.03 (0.99, 1.08)</td>
<td>49</td>
<td>1.03 (0.99, 1.08)</td>
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<tr>
<td>Li</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>PB</td>
<td>MassARRAY</td>
<td>629</td>
<td>411</td>
<td>1.03 (0.99, 1.08)</td>
<td>340</td>
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<tr>
<td>Safaeian (NCI)</td>
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<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>HumanHap</td>
<td>322</td>
<td>529</td>
<td>1.03 (0.99, 1.08)</td>
<td>51</td>
<td>1.03 (0.99, 1.08)</td>
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<tr>
<td>Safaeian (NIOSH)</td>
<td>2013</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>HumanHap</td>
<td>300</td>
<td>470</td>
<td>1.03 (0.99, 1.08)</td>
<td>25</td>
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<tr>
<td>Safaeian (PLCO)</td>
<td>2013</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>HumanHap</td>
<td>133</td>
<td>237</td>
<td>1.03 (0.99, 1.08)</td>
<td>30</td>
<td>1.03 (0.99, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Safaeian (ATBC)</td>
<td>2013</td>
<td>Finland</td>
<td>Caucasian</td>
<td>PB</td>
<td>HumanHap</td>
<td>37</td>
<td>61</td>
<td>1.03 (0.99, 1.08)</td>
<td>13</td>
<td>1.03 (0.99, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Safaeian (AHS)</td>
<td>2013</td>
<td>America</td>
<td>Caucasian</td>
<td>PB</td>
<td>HumanHap</td>
<td>18</td>
<td>26</td>
<td>1.03 (0.99, 1.08)</td>
<td>10</td>
<td>1.03 (0.99, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Jin</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>PB</td>
<td>MassARRAY</td>
<td>433</td>
<td>589</td>
<td>1.03 (0.99, 1.08)</td>
<td>24</td>
<td>1.03 (0.99, 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction; MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; TaqMan: TaqManSNP; NCI: the National Cancer Institute; NIOSH: the National Institute for Occupational Safety and Health; PLCO: the Prostate, Lung, Colorectal and Ovarian; ATBC: the Alpha-Tocopherol, Beta-Carotene; AHS: the Agricultural Health Study; HWE: Hardy-Weinberg equilibrium.

## Table 2. Regulator of telomere elongation helicase 1 rs6010620 polymorphism and glioma risk

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Source of control</th>
<th>GG versus AA</th>
<th>GG+AG versus AA</th>
<th>GG versus AA+AG</th>
<th>G versus A</th>
<th>AG versus AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>Population</td>
<td>1.04 (0.98, 1.10)</td>
<td>1.02 (0.98, 1.07)</td>
<td>1.00 (1.00, 1.07)</td>
<td>1.06 (1.02, 1.10)</td>
<td>1.09 (1.00, 1.05)</td>
</tr>
<tr>
<td>Asian</td>
<td>Population</td>
<td>1.31 (1.09, 1.57)</td>
<td>1.10 (1.00, 1.22)</td>
<td>1.04 (0.99, 1.08)</td>
<td>1.05 (0.99, 1.08)</td>
<td>1.01 (0.99, 1.02)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Hospital</td>
<td>1.05 (0.98, 1.11)</td>
<td>1.02 (0.98, 1.07)</td>
<td>1.00 (1.00, 1.07)</td>
<td>1.06 (1.02, 1.10)</td>
<td>1.03 (0.99, 1.05)</td>
</tr>
<tr>
<td>Asian</td>
<td>Hospital</td>
<td>1.11 (0.99, 1.25)</td>
<td>1.07 (0.99, 1.16)</td>
<td>1.05 (1.01, 1.10)</td>
<td>1.09 (1.02, 1.16)</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Mixed</td>
<td>1.03 (0.83, 1.29)</td>
<td>1.02 (0.85, 1.22)</td>
<td>1.00 (1.00, 1.07)</td>
<td>1.06 (1.03, 1.10)</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
<tr>
<td>Asian</td>
<td>Mixed</td>
<td>1.06 (1.00, 1.11)</td>
<td>1.03 (0.99, 1.08)</td>
<td>1.01 (1.00, 1.07)</td>
<td>1.07 (1.03, 1.10)</td>
<td>1.05 (0.99, 1.07)</td>
</tr>
</tbody>
</table>

Ph: P-value of heterogeneity test.
rs6010620 and glioma risk. The pooled ORs were performed for GG vs. AA, GG+AG vs. AA, GG vs. AA+AG, G vs. A, AG vs. AA. In the subgroup analysis, statistical analysis was conducted in Asians and Caucasians. Z test was used to evaluate whether the pooled ORs were significant. P<0.05 was considered statistically significant. Heterogeneity assumption was testified by Q test. The pooled ORs were calculated by the fixed-effects model when P (heterogeneity) >0.05. Otherwise, the random-effects model was used. We adopted Begg’s funnel plots and Egger’s test to assess the publication bias. HWE was checked by χ² test. The sensitivity analysis was conducted repeatedly by precluding a single study every time in multiple genetic models. Statistical analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Articles search and the characteristics of the studies

As listed in Figure 1, a total of 143 relevant articles were identified. According to the inclusion criteria, 124 studies were excluded: 6 studies for overlapping data, 79 studies for unrelated research, 17 studies for no control group and 22 studies for no locus. Finally, 19 studies were considered acceptable and included into our meta-analysis. The characteristics of nineteen studies were shown in Table 1.
Meta analysis results

As shown in Table 2, the overall ORs with 95% CIs demonstrated that the presence of regulator of telomere elongation helicase 1 rs6010620 polymorphism with GG genotype or G allele was an increased factor for glioma risk (GG vs. AA+AG: OR=1.28, 95% CI=1.14-1.43; G vs. A: OR=1.07, 95% CI=1.03-1.10). In the subgroup analysis by ethnicity, findings were similar in Asians (GG vs. AA: OR=1.31, 95% CI=1.09-1.57; G vs. A: OR=1.13, 95% CI=1.04-1.23) and Caucasians (GG vs. AA+AG: OR=1.25, 95% CI=1.11-1.41; G vs. A: OR=1.06, 95% CI=1.02-1.09). In the subgroup analysis by source of control, elevated risk was observed with G allele based on population (G vs. A: OR=1.06, 95% CI=1.02-1.10) and hospital (G vs. A: OR=1.09, 95% CI=1.02-1.16) (Figures 2, 3).

Sensitivity analysis

The sensitivity analysis was conducted repeatedly by excluding a single study every time in multiple genetic models. The results showed that the corresponding pooled ORs were not altered, suggesting that our meta-analysis results were reliable (data not shown).

Publication bias

We used funnel plot and Egger’s test to estimate the publication bias of literature. As
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have reported that three locus (rs2297440, rs2853-676, and rs6010620) of regulator of telomere elongation helicase 1 are associated with the increased risk of glioma [28]. Walsh et al. also have found that regulator of telomere elongation helicase 1 rs6010620 serves as risk factor for glioma based on Caucasian population [29].

The present meta-analysis, with 8541 cases and 14226 controls, was conducted to derive a more precise assessment between regulator of telomere elongation helicase 1 rs6010620 and glioma susceptibility. The results suggested that the GG genotype of regulator of telomere elongation helicase 1 rs6010620 was significantly associated with the risk for glioma under recessive model. Further subgroup analysis was based on ethnicity and source of control, and the G allele also played an important role in the pathogenesis of glioma.

Overall, our meta-analysis presented regulator of telomere elongation helicase 1 rs6010620 as the genetic-susceptibility factor for glioma. However, there were several limitations that should be addressed. Firstly, we failed to discuss how the risk G allele of rs6010620 polymorphism affect the development of glioma. Further studies are required to research this issue. Secondly, the results were based on unadjusted estimates, which might affect the validity of the association. Finally, lack of considering the effects of other genetic or environmental factors on glioma risk might make our results biased. Therefore, further well-designed investigations based on larger scales are needed to clarify this point of view.

Disclosure of conflict of interest

None.

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Discussion

Glioma originating from glial cells is the most common primary tumors of the central nervous system, and it accounts for the vast majority of the malignant brain tumors [10-14]. The incidence rate of glioma is increasing in a number of Asian countries, especially in China. According to the Health Statistics Yearbook 2009 of China, the annual mortality rate of glioma in China was approximately 3.13 per 100,000 population during 2008 [15]. For the etiology, genetic factors had strong effects on the development of glioma [16-21]. Regulator of telomere elongation helicase 1 is an essential DNA helicase that disassembles a variety of DNA secondary structures to maintain telomere integrity [22-25]. As we all know, regulator of telomere elongation helicase 1 had many polymorphic sites and rs6010620 was the most widely studied one. Regulator of telomere elongation helicase 1 polymorphisms play important roles in cancer pathogenesis, since the mutation in regulator of telomere elongation helicase 1 could cause telomere dysfunction [26] that was associated with risk of various cancers [27]. For regulator of telomere elongation helicase 1 polymorphisms, Jin et al.
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References


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