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# Mapping genetic factors in high-grade glioma patients

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ABSTRACT

*Background:* Tumor location, which serves as a prognostic factor for high-grade gliomas, may reflect the molecular and genetic phenotype of tumor initiate cells and thus predict tumor origin. Therefore, the purpose of this study was to combine radiographic atlases and tumor biomarkers through a voxel-based neuroimaging approach.
*Methods:* Preoperative MRIs were collected from 65 newly diagnosed patients with histologically confirmed high-grades gliomas. These samples were analyzed for TP53 mutations and MMP-9.PTEN, MGMT, EGFR and IDH1 statuses using a statistical voxel-based lesion-symptom mapping (VLSM) method, which correlates the anatomical location of HGGs with their molecular profile.
*Results:* VLSM analysis identified P53, Wild-type IDH and EGFR overexpression mutations in the white matter of the periventricular region in the left hemisphere, which can be predicted by a short overall survival from the time of diagnosis. The lack of MGMT promoter methylation deep in the right frontal lobe region indicates a poor prognosis.
*Conclusions:* Our study demonstrates that different molecular phenotypes are related to specific brain regions. In addition, the structural MRI and genetic profile-based analysis of brain regions associated with survival-associated factors could be used in planning glioma operations and clinical survival predictions.
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## 1. Introduction

High-grades gliomas (HGGs), defined by the World Health Organization as grade III and IV gliomas, constitute the majority of malignant primary brain tumors [1,2]. Patients with glioblastoma multiforme (GBM, WHO Grade IV) who undergo the maximum safe tumor resection and are administered standard radiochemotherapy with temozolomide (TMZ) achieve a median survival of only 14.6 months [3]. Glioblastomas can develop *de novo* or via the progression of a grade III glioma, which is typically associated with a five-year survival rate of 24% [4].

Overexpression or mutations of genomic biomarkers in the core pathways associated with high-grade gliomas can be correlated with poor patient prognosis. Mutations in TP53 and PTEN and amplification of EGFR are early events in the progression of HGGs [5–7]. IDH1/2 mutations and MGMT promoter methylation status may provide information regarding the prognosis and response to chemotherapy [8,9]. Tumor location may be genetically related to the cellular origin of gliomas, and tumor distribution is one of the most important characteristics for predicting the development of a glioma and the prognosis of a patient [10]. However, the relationship between tumor origin/location and these molecules has not been investigated.

Voxel-based lesion–symptom mapping (VLSM) has been increasingly advocated for analyzing correlations between behavioral deficits and the brain lesion sites associated with those deficits. Other studies also found VLSM to be an efficient method for mapping the brain regions responsible for attention, motion detection and motor deficits [11]. VLSM can provide voxel-level proof of HGG [12]. In this study, we used the VLSM method to analyze statistical correlations between genomic biomarkers and tumor intensity and to verify the location of survival-associated molecules in high-grade glioma patients.

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**Table 1**
Characteristics of the 65 patients recruited.

| Subjects | Values |
|---|---|
| Total patients | 65 |
| Male | 37(56.9%) |
| Female | 28(43.1%) |
| Median age (years) | 42(23–69) |
| Tumor location | |
| Left hemisphere | 28(43.1%) |
| Right hemisphere | 32(49.2%) |
| Bilateral hemisphere | 5 (7.6%) |
| Histology | |
| WHO grade III | 19(29.2%) |
| WHO grade IV | 46(71.8%) |

## 2. Methods

### 2.1. Participants and characteristics

Between September 2014 and May 2015, we recruited 65 newly diagnosed patients with histologically confirmed high-grades gliomas from the glioma center associated with West China Hospital. The patients enrolled in this study met the following inclusion criteria: 1) pathological diagnosis of HGG; 2) no medical history of biopsy or radiotherapy; 3) no previous cerebral damage reported in their medical history; and 4) preoperative DICOM data available for analysis. The ethics committee of the hospital approved this study, and informed consent was obtained from all of the patients. The characteristics of the eligible patients are summarized in Table 1.

### 2.2. MRI data pre-processing and tumor registration

All of the patients (n = 65) underwent an MRI enhancement brain scan using an Avanto 1.5T (Siemens, Erlangen, Germany) scanner. The T1-contrast image parameters included the following: repetition time (ms), 550; slice thickness (mm), 5; slice spacing (mm), 7.9; image columns, 408; and flip angle, 90. Hyper-intense regions in the T1-contrast image were defined as regions of interest (ROIs), which were independently delineated by two associated professors (W. X. and L. YH). MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron/install) was used for lesion mapping. Images from each patient were manually realigned prior to registration in a high-resolution (1.0-mm isotropic) brain atlas (Montreal Neurological Institute 152 [MNI152]) using a normalizing algorithm provided by SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12).

### 2.3. Immunohistochemical analysis for biomarkers

Immunohistochemical analyses of six markers (mutant P53, PTEN, MMP-9, IDH1, EGFR and MGMT methylation status) were performed using formalin-fixed, paraffin-embedded tissue sections following the manufacturer's recommended protocol. Each slide stained for these markers was reviewed by two independent neuropathologists, and the final score in cases of discrepancies was determined by discussion until consensus was reached. The criteria were the following: −, negative; +, isolated positive cells (<5%); ++, clusters of positive cells (5%–10%); +++, 10%–30% positive cells; ++++, mostly positive cells (>30%) (Fig. 1).

### 2.4. Voxel-based neuroimaging analysis

A VLSM analysis was performed using the npm software. (http://www.mccauslandcenter.sc.edu/mricro/mricron/). After data pre-processing, lesion maps were loaded into the software. We first

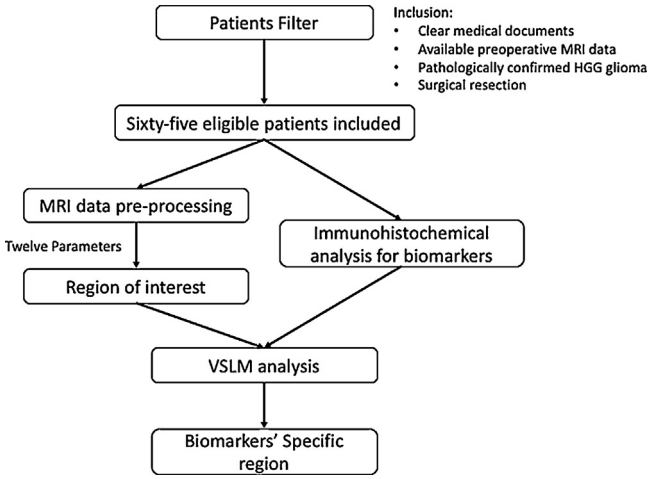


**Fig. 1.** Flow diagram of study design. Patients meet the inclusion criteria were included in this study, their pre-operative DICOM MRI data were pre-processed and normalized, then the region of interest(ROI) were drawn. Finally, the VLSM analysis were based on the ROI and immunohistochemical results.

**Table 2**
Molecular biomarkers distribution of eligible patients in this study.

| Patients Characteristics | Grade 3 (%) | Grade 4(%) | p Value[a] |
|---|---|---|---|
| Total patients | 19 | 46 | |
| Mean age | 41.4(17–71) | 42.8(17–70) | 0.235 |
| *TP53 (+/−)* | 17/2 | 44/2 | 0.584 |
| *PTEN (+/−)* | 7/12 | 21/25 | 0.514 |
| *MMP-9 (+/−)* | 6/13 | 25/21 | 0.095 |
| *IDH1 (+/−)* | 11/8 | 4/42 | 0.000 |
| *EGFR (+/−)* | 5/14 | 12/34 | 0.984 |
| *MGMT (+/−)* | 6/13 | 24/22 | 0.130 |

[a] T test for mean age and chi-square test for molecule profile.

overlapped the normalized region of interest for all of the included patients and then constructed a power map. We subsequently described the lesion maps and named the behavioral performance measures. For binomial data, the presence of a deficit was scored as 0, whereas healthy performance was scored as 1. For continuous data, higher scores reflect better performance. After discussions with the pathologist and confirming that the test power was >0.8 (indicating that each subgroup had at least 13 patients), we analyzed the TP53 mutation results as continuous data with scores from 0 to 3. All of the other biomarkers and epileptic symptoms were analyzed as binomial data. For the statistical analysis of continuous data, we used a non-parametric test (permuted Brunner-Munzel rank order statistic), whereas for the analysis of binomial data, we used Liebermeister's measure (a more sensitive binomial test than Chi-Squared or Fisher's Exact test, see Seneta and Phipps, 2001; Phipps, 2003) [13,14]. The results were viewed using MRICRON software. Permutation thresholding values were determined by randomly relabeling and resampling the data. To compute the maximum observed statistic within the entire brain volume, 1000 permutations were performed.

## 3. Results

A total of 65 patients with newly diagnosed and histologically confirmed high grade gliomas during the aforementioned period were included in the study, and their demographic characteristics and symptoms are summarized in Tables 1 and 2. The study consist of 37 (56.9%) males and 28 (43.1%) females, and the median age was 42. The tumor was localized in the left hemisphere in 28 cases (43.1%) and in the right hemisphere in 32 cases (49.2%), and 5 patients were diagnosed with bilateral glioma. IDH1 mutations

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