Oligodendroglial tumours: subventricular zone involvement and seizure history are associated with CIC mutation status

Zhenyin Liu†, Hongsheng Liu†, Zhenqing Liu and Jing Zhang*

Abstract

Background: CIC-mutant oligodendroglial tumours linked to better prognosis. We aim to investigate associations between CIC gene mutation status, MR characteristics and clinical features.

Methods: Imaging and genomic data from the Cancer Genome Atlas and the Cancer Imaging Archive (TCGA/TCIA) for 59 patients with oligodendroglial tumours were used. Differences between CIC mutation and CIC wild-type were tested using Chi-square test and binary logistic regression analysis.

Results: In univariate analysis, the clinical variables and MR features, which consisted 3 selected features (subventricular zone [SVZ] involvement, volume and seizure history) were associated with CIC mutation status (all \( p < 0.05 \)). A multivariate logistic regression analysis identified that seizure history (no vs. yes odd ratio [OR]: 28.960, 95% confidence interval [CI]: 2.625–319.49, \( p = 0.006 \)) and SVZ involvement (SVZ- vs. SVZ+ OR: 77.092, \( p = 0.003 \); 95% CI: 4.578–1298.334) were associated with a higher incidence of CIC mutation status. The nomogram showed good discrimination, with a C-index of 0.906 (95% CI: 0.812–1.000) and was well calibrated. SVZ- group has increased (SVZ- vs. SVZ+, hazard ratio [HR]: 4.500, \( p = 0.04 \); 95% CI: 1.069–18.945) overall survival.

Conclusions: Absence of seizure history and SVZ involvement (−) was associated with a higher incidence of CIC mutation.

Keywords: Oligodendroglial Tumours, CIC mutation, Subventricular zone involvement, Logistic regression, Seizure history
prognoses might be linked to neuronal stem cells (NSCs), located in the subventricular zone (SVZ) [8, 16, 17].

To date, although several studies have evaluated MRI characteristics as they relate to IDH/1p19q status [18, 19], no study has investigated associations between CIC mutation status and MR imaging features in oligodendrogial tumours. Radiological detection of CIC mutation status may facilitate the preoperative prediction of a patient’s prognosis. Therefore, this paper reports preliminary research that can be used to determine the associations between CIC gene mutation status, MR characteristics and clinical features.

**Methods**

**Patient population**

All patient data was acquired from the published The Cancer Genome Atlas LowGrade Glioma (TCGA-LGG) project and within this publication it is stated “Specimens were obtained from patients, with appropriate consent from institutional review boards” (http://cancergenome.nih.gov/). The clinical files of oligodendrogial tumours were downloaded from the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/dataAccessMatrix.htm; updated: 2018-08-23). MR data were provided by TCIA (updated: 2014-09-04). TCGA and TCIA are publicly available databases that contain no linkage to patient identifiers. All patients must meet the following criteria to enter our study: available pathologic diagnosis of oligodendrogial tumours (oligodendroglioma or oligoastrocytoma) from TCGA; available CIC mutation status (CIC mutation or CIC wild-type) from TCGA [20] (extracted from a previous study [N Engl J Med. 2015; 372 (26):2481–2498]); and available MR images (T1WI, T2WI, Flair and post-contrast) from TCIA. Finally, 59 patients with oligodendrogial tumours were used in this institutional review board approval–exempt study.

**Image feature analysis**

The MR images were presented to two radiologists for interpretation and measurement and in cases of disagreement a consensus was reached after discussion. Both radiologists were blind to CIC mutation status and clinical information. The following 7 qualitative MR imaging features [11, 12, 21, 22] were evaluated: (1) volume (< 60 cm³ vs. ≥60 cm³); (2) multifocal (no vs. yes); (3) intratumoural haemorrhaging (no vs. yes); (4) enhancing margin (well defined vs. poorly defined); (5) necrosis (no vs. yes); (6) proportion of contrast-enhanced tumour (<5% vs. ≥5%); and (7) SVZ Involvement (no vs. yes). The tumours that were located in close contact with the SVZ were classified as SVZ+, while the tumours that were located distantly from the SVZ were classified as SVZ–.[17]

**Statistical analysis**

Differences between CIC mutation and CIC wild-type were tested using the Chi-square test and binary logistic regression analysis (version 22.0; SPSS Company, Chicago, IL). Odd ratios (OR) and 95% confidence intervals (CI) are reported. The area under the receiver operator characteristic curve (AUC) was estimated for prediction of CIC gene mutation status. The sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of the model in the prediction of CIC mutations were

![Fig. 1 Tumor (T2-weighted MR images) localization in the cortex without subventricular zone involvement (a). Tumor (T2-weighted MR images) with infiltration of the subventricular zone (b)](image)
obtained. Survival analysis (SVZ- vs. SVZ+) was estimated using the Cox proportional hazards models. Hazard ratios (HR) and 95% CI are reported. The statistical significance threshold was set at a $P$-value of 0.05 (two-sided) to indicate statistical significance.

**Results**

Our series of 59 patients (45.4 ± 14.0 years, range: 18–74 years) included 29 men (49.2%) and 30 (50.8%) women. CIC mutations were found in 10 (16.9%) of 59 patients. There were 35 patients (59.3%) with tumours that involved the SVZ (Fig. 1). Specifically, 8 tumours involved the frontal horn, 5 the body, 1 the occipital horn, 17 the temporal horn and 4 others. The cohort mean OS was 37.5 months (range: 0.03–156.11 and median = 21.4), and 44 patients were still alive (74.6%) at the end of the study while 15 were deceased (25.4%). Clinical data are summarized in Table 1 and Additional file 1: Table S1.

In univariate analysis, the clinical variables and MR features, which consisted of three selected features (SVZ involvement, volume and seizure history) were significantly associated with CIC mutation status (all $P < 0.05$). We demonstrated that a smaller tumour volume (OR: 9.100, $P = 0.004$), SVZ-(OR: 20.400 $P = 0.006$) and a history absent of seizures (OR: 6.462, $P = 0.014$) were associated with a significantly higher incidence of CIC mutations (Table 1 Fig. 2).

In multivariate logistic regression analysis, only two risk factors were significant independent predictors (Table 2). We demonstrated that seizure history (no vs. yes OR: 28.960, 95CI: 2.625–319.49, $P = 0.006$) and subventricular zone involvement (SVZ- vs. SVZ+ OR: 77.092, $P = 0.003$; 95% CI: 4.578–1298.334) were associated with a significantly higher incidence of CIC mutations (Table 1 Fig. 2).

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calibrated (Fig. 3). The sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of this model in the prediction of CIC mutations were 0.90, 0.71, 3.09 and 0.14, respectively. Subventricular zone involvement (−) of oligodendrogial tumours in combination with absence of seizure history may therefore be used to better prognosticate CIC mutation status than the use of each variable alone (Fig. 4).

Patients (follow up: 0.03–156.11 months) with SVZ− had a longer median overall survival (133.6 vs.65.7)

Table 2 binary logistic regression analysis of prognostic factors for CIC mutation status

|                        | Wald  | Sig.   | OR   | 95.0% CI for OR Lower | Upper   |
|------------------------|-------|--------|------|-----------------------|---------|
| Subventricular Zone Involvement | 9.095 | 0.003* | 77.092 | 4.578                 | 1298.334 |
| Seizure History        | 7.551 | 0.006* | 28.960 | 2.625                 | 319.49  |
| Constant                | 14.378| 0.000* | 0.003 |                       |         |

*P < 0.05

Fig. 3 Multivariate analysis showed that absence of seizure history and SVZ involvement (−) was associated with a higher incidence of CIC mutation. The nomogram showed good discrimination, with a C-index of 0.906 (95% CI: 0.812–1.000) and was well calibrated.
months (SVZ- vs. SVZ+, hazard ratio (HR): 4.500, \( P = 0.04 \); 95% CI: 1.069–18.945) than patients with SVZ+ (Fig. 5). SVZ+ tumors were significantly larger than SVZ- tumors (181 ± 92.1 cm\(^3\) vs. 117 ± 116 cm\(^3\), \( P < 0.05 \)).

**Discussion**

Molecular genetic studies demonstrated distinct glioma entities with specific epigenetic and genetic profiles [23]. Some oligoastrocytomas and most oligodendrogliomas are characterized by a typical and unique unbalanced translocation, der (1, 19), resulting in a 1p/19q co-deletion (codeletion of 1p and 19q). Candidate tumour suppressor genes (TSGs) targeted by these losses, including FUBP1 on 1p31.1 and CIC on 19q13.2, were only recently discovered [10]. CIC-mutant oligodendrogial tumours are also linked to better prognoses [8, 9].

There are a number of studies regarding the relationship between imaging features and gene mutations. Rios Velazquez E et al. [24] confirmed that quantitative features related to intratumour heterogeneity that were able to successfully discriminate (AUC = 0.69) between EGFR- and EGFR+ lesions. Brendle C et al. [25] showed that the differentiation of high-grade gliomas and low-grade gliomas (sensitivity: 100%; specificity: 80%) is made possible by the dynamic contrast-enhanced MR perfusion parameter Ve (\( P = 0.024 \)), while arterial spin labelling perfusion shows the potential for the discrimination of the ATRX and IDH mutation statuses (sensitivity: 75%; specificity: 88%, \( P = 0.014 \)). Dagher J [26] implied that wild-type von Hippel-Lindau (VHL) renal cell carcinomas were associated with lymph nodal metastases. Rizzo S [27] found that a pleural effusion related to ALK mutations while nodules located in non-tumour lobes or round lesion shapes were related to a KRAS mutation in subgroups of non-small cell lung cancer patients. So far, no study has investigated associations between CIC mutation status and MR imaging features in oligodendrogial tumours. This study suggests that SVZ involvement and seizure history can be conveniently used to facilitate the prediction of CIC mutation status.

The subventricular zone has been associated with the origination and development, as well as the biological behaviour of LGGs [22]. Recently, limited studies have reported associations between SVZ involvement and patient prognosis. Nakagawa Y et al. [28] implied that the loss of 19q and lack of SVZ+ might be prognostic for longer survival. Liu S et al. [22] reported that multivariate analysis showed that a shorter distance between the tumor centroid and the SVZ (19q) was significantly associated with poor overall survival in SVZ-involved patients (low-grade astrocytoma). Liu S et al. [22] also reported that a longer distance between the SVZ and the tumour centroid was significantly related to better overall survival in SVZ-involved LGG patients. Adeberg S et al. [8] confirmed that the tumour location with regard to the subventricular zone is related to a patient’s prognosis (\( P < 0.05 \)).

Nomograms are user-friendly tools that give relative contexts and probabilities of cancer prognoses [11].
the present study, we constructed three models for the preoperative prediction of CIC mutation statuses in oligodendroglial tumours. ROC curve analysis showed that use of seizure history combined with SVZ involvement (AUC = 0.906) was superior to simply the use of seizure history (AUC = 0.725) or SVZ involvement alone (AUC = 0.804). The discriminatory power of the nomogram which combined SVZ involvement and seizure history was also very strong and well calibrated.

The limitations of our study included the retrospective nature of our data collection, the relatively limited number of cases (n = 59) and the automatic imaging feature extraction not being implemented. In addition, we do not know whether re-classification by an expert neuropathologist has been performed, however, similar to other papers (2017–2019 more than 250 articles) published using this dataset, we therefore believe our conclusions are not largely influence by such factors. Further study should be conducted by using a larger pool of oligodendroglial tumours patients with the use quantitative image analysis tools being required [29]. The newly emerged field of radiogenomics allows specific MR imaging phenotypes to be linked with gene expression profiles. Further work is needed to better define the relationships identified in our study and to explore additional relationships (SVZ involvement and CD133, SVZ involvement and CD44, SVZ involvement and MMPs).

Conclusions
In conclusion, this study presents that SVZ involvement (−) and absence of seizure history may therefore be used to facilitate the prediction of CIC mutation status. Patients with SVZ− had a longer median overall survival months than patients with SVZ+. This work represents a practical application of imaging findings for personalized medicine. External validation of this model in other cohorts of patients is needed.

Additional file
Additional file 1: Table S1. Clinical data of this study. (XLS 71 kb)

Abbreviations
AUC: Area under the curve; CI: Confidence interval; CIC: Capicua transcriptional repressor; HR: Hazard ratio; IDH: Isocitrate dehydrogenase; LGG: Low-grade gliomas; NLR: Negative likelihood ratio; NSCs: Neuronal stem cells; OR: Odds ratio; PLR: Positive likelihood ratio; SVZ: Subventricular zone; TCIA: The Cancer Imaging Archive; TSGs: Tumor suppressor genes

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None.

Authors’ contributions
ZYL and HSL performed the statistical analysis and drafted the manuscript, JZ, QJL, HSL and ZYL participated in the design of the study and helped to draft the manuscript, JZ and ZYL collected the data, JZ and ZYL helped to perform the statistical analysis, JZ conceived of the study and participated in the design of the study. All authors read the approved the final manuscript.

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Availability of data and materials
All data generated or analyzed in this study is included in this published article and its Additional files.

Ethics approval and consent to participate
All patient data was acquired from the published The Cancer Genome Atlas Low Grade Glioma (TCGA-LGG) project and within this publication it is stated “Specimens were obtained from patients, with appropriate consent from institutional review boards”. (http://cancergenome.nih.gov/).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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