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IDH mutations but not *TERT*p mutations are associated with seizures in lower-grade gliomas

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Abstract

Glioma is the most common malignant tumor in the central nervous system (CNS). Lower-grade gliomas (LGG) refer to Grade II and III gliomas. In LGG patients, seizure often appears as an initial symptom and play an important role in clinical performance and quality of life of the patients. To date, the relationship between the onset of seizures and the molecular pathology in gliomas is still poorly investigated. In this study, we investigate the potential relationship between isocitrate dehydrogenase (IDH)/telomerase reverse transcriptase promoter (TERTp) mutations and preoperative seizures in patients with LGG. 289 adult LGG patients were enrolled in this study. Data of clinical characteristics and molecular pathology were acquired. Sanger sequencing was used to detect IDH/TERTp mutations. Chi-square test was performed to determine if the IDH/TERTp mutations were associated with seizures and seizure types. In 289 LGG patients, preoperative seizures accounted for 25.3% (73/289), IDH mutations accounted for 34.3% (99/289), and TERTp mutations accounted for 44.3% (128/289). The correlation analysis demonstrated that IDH mutation is a significant factor influencing the occurrence of tumor-related epilepsy ($P < .001$, chi-square test). On the other hand, the statistical analysis revealed no significant correlation between TERTp mutations and seizure in LGG patients ($P = .102$, chi-square test). The tumor-related epilepsy rates vary among different subgroups according to IDH/TERTp mutations. However, there is no definite correlation between the IDH ($P = 1.000$, chi-square test)/TERTp ($P = .613$, chi-square test) mutations and the types of epileptic seizure. IDH mutations are more common in preoperative LGG patients with epileptic symptoms, suggesting that this mutation is positively correlated with seizures. However, there was no significant correlation between TERTp mutations and seizures. Different molecular pathologic types based on IDH/TERTp have different incidences of tumor-associated epilepsy in LGGs.

Abbreviations: 2Hg = 2-hydroxyvalerate, CNS = central nervous system, FFPE = formalin-fixed paraffin embedded, HMGB1 = high-mobility group box 1, *IDH* = isocitrate dehydrogenase, LGG = Lower-grade gliomas, NMDA = N-methyl-D-aspartate, *TERT*p = telomerase reverse transcriptase promoter, WHO = World Health Organization.

Keywords: glioma, *IDH*, seizure, *TERT*

1. Introduction

Glioma is the most common neuroepithelial tumors originating from the supporting glial cells of the central nervous system (CNS).[1] Epilepsy is a chronic cerebral dysfunction syndrome caused by a variety of causes. It is characterized by episodic, abrupt, and transient brain disorders caused by repeated supersynchronous discharges of cerebral nerve cells.[3] In lower-grade gliomas (LGG) patients, epilepsy often manifest itself as an initial symptom and has a negative impact on the patient's neurocognitive function and quality of life.[5] Most LGG patients (65%–90%) have symptomatic seizures.[6]

The isocitrate dehydrogenase *(IDH)1* and *IDH2* mutations occur in more than 70% of patients with LGG[9] and have been identified as potential biomarkers for glioma-associated epilepsy.[10] The telomerase reverse transcriptase promoter *(TERT*p) mutation is another molecular marker of glioma discovered in recent years. The mutations are mainly concentrated in C228T and C250T sites in the promoter region. The total mutation rate is about 50% in primary glioblastoma. In secondary glioblastoma, the proportion of *TERT*p mutation can reach 70% to 80%.[14] However, as far as we know, the study exploring the relationship between *TERT*p mutation and tumor-related epilepsy is not reported by far. A better understanding of the relationship between molecular pathology such as *IDH/TERT*p mutations and seizures in LGG patients has a very important clinical and social value for setting therapeutic regimen and improving the life quality of the patients. We aimed to investigate the potential relationship between *IDH/TERT*p mutations and

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preoperative seizures in patients with LGG and to reveal whether the *IDH/TERT*p mutations are related to the onset of seizure and seizure types.

2. Materials and methods

2.1. Patients and specimen

Two hundred eighty-nine LGG patients undergoing surgery in the Department of Neurosurgery at the First Affiliated Hospital of Zhengzhou University from 2012 to 2015 were enrolled in this study. Inclusion criteria of the series were:

(1) all patients were 18 years of age or older;
(2) included only World Health Organization (WHO) defined Grade II or III gliomas (astrocytoma, oligodendroglioma, and oligoastrocytoma);
(3) patients who have undergone secondary resection or only biopsy are excluded.

Formalin-fixed paraffin embedded (FFPE) tissues, clinical data, and follow-up data were acquired. All cases were stained with hematoxylin & eosin (H&E) and centrally reviewed according to the 2010 WHO criteria by 2 senior neuropathologists of the First Affiliated Hospital of Zhengzhou University.[2] Clinical and follow-up data were collected from medical charts, central radiological systems of the hospitals, out-patient clinics, and telephone interviews. All the above-mentioned patients were approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and written informed consents was obtained from the patients (or their families).

2.2. Definition of seizure types

Of the 289 patients enrolled in this study, 73 had preoperative epilepsy symptoms. According to the patient's history and symptoms at admission and the seizure classification scheme proposed by the International League Against Epilepsy, the type of epilepsy was divided into partial seizures and generalized seizures.[15,16] We obtained patient case data from the Department of Medical Records of the First Affiliated Hospital of Zhengzhou University, including name, chief complaint, current medical history, record of course of disease, imaging report and image, and surgical records. And we obtained the characteristic information about the seizure of patients. Patients with short duration (less than 1 min), sudden onset and end, and conscious or varying degrees of loss of consciousness were defined as simple or complex partial seizures. Patients with loss of consciousness and generalized convulsions were defined as generalized seizures. In this study, there were 27 patients with partial seizures and 46 patients with general seizures according to previous criteria.

2.3. Analysis of molecular markers

Tumor DNA was extracted from FFPE tissue samples in all 289 cases in this cohort. Mutational hotspots of IDH at codon 132 and 172 were evaluated by direct sequencing as previously reported.[25,36] Mutational hotspots [chr5, 1, 295, 228 (C228T) and 1, 295, 250 (C250T)] in the TERT promoter region were evaluated by direct sequencing as previously reported[25,37].

2.4. Statistical analyses

All statistical analyses were conducted using SPSS version 21.0. The univariate analysis was performed using a chi-square test to determine whether the *IDH/TERT*p mutations were associated with preoperative epilepsy in patients with LGG. Using multivariate logistic regression analysis, molecular pathology, tumor location, and epileptic seizure types were analyzed to determine whether *IDH/TERT*p mutations were involved in premonitory seizure. At the same time, the internal relationship between *IDH/TERT*p mutations and epileptic seizure types was analyzed by the same method.

3. Results

3.1. Clinical and molecular characteristics of patients

Out of 295 total patients, there were 165 males and 124 females in the series with a male to female ratio of 1.44:1, and the preoperative seizures accounted for 25.3%(73/289). Including 154 cases of astrocytoma and 135 cases of oligodendroglioma and oligoastrocytoma. The mean age at diagnosis was 48.7 years. The mean duration of follow-up was 5.9 years. *IDH* mutations were found in 99 (34.3%) cases while mutations in the *TERT*p mutations were found in 128 (44.3%) cases. Among the 289 LGG patients enrolled in the study, 99 had *IDH* mutations, including 94 (94.95%) with *IDH1* mutation, 5 (5.05%) with *IDH2* mutation, 96 (96.97%) with R132 mutation, and 3 (3.03%) with R172 mutation. 128 patients had *TERT*p mutations, including 95 (74.22%) with C228T mutation, 33 (25.78%) with C250T mutation. The clinical and molecular characteristics of these patients are summarized in Table 1.

3.2. Associations of preoperative seizures with IDH/TERTp mutation status

Among 289 LGG patients, preoperative seizures accounted for 25.3% (73/289), *IDH* mutations accounted for 34.3% (99/289), and *TERT*p mutations accounted for 44.3% (128/289). The correlation analysis between *IDH* mutation and preoperative seizures in patients with LGG (Fig. 1**A**, $P < .001$, $X^2 = 20.816$, $v = 1$, chi-square test, Table 2) demonstrated that *IDH* mutation is a significant factor influencing the occurrence of tumor-related epilepsy. On the other hand, the statistical analysis revealed no significant correlation between *TERT*p mutations and seizure (Fig. 1**B**, $P = .102$, $X^2 = 2.978$, $v = 1$, chi-square test, Table 2). Multivariate logistic regression analysis was used to determine the potential association between *IDH* mutations

Table 1

Clinical and molecular characteristics of 289 patients.

Parameter	Total (%)	Seizure (%)	No seizure (%)
Number of patients	289	73	216
Gender			
Male	165 (57.1)	45 (61.6)	120 (55.6)
Female	124 (42.9)	28 (38.4)	96 (44.4)
Mean age, year	48.7	48.7	48.7
Histopathology			
Astrocytoma	154 (53.3)	39 (53.4)	115 (53.2)
Oligodendroglioma and oligoastrocytoma	135 (46.7)	34 (46.6)	101 (46.8)
IDH status			
Mutation	99 (34.3)	41 (56.2)	58 (26.9)
No mutation	190 (65.7)	32 (43.8)	158 (73.1)
*TERT*p status			
Mutation	128 (44.3)	26 (35.6)	102 (47.2)
No mutation	161 (55.7)	47 (64.4)	114 (52.8)

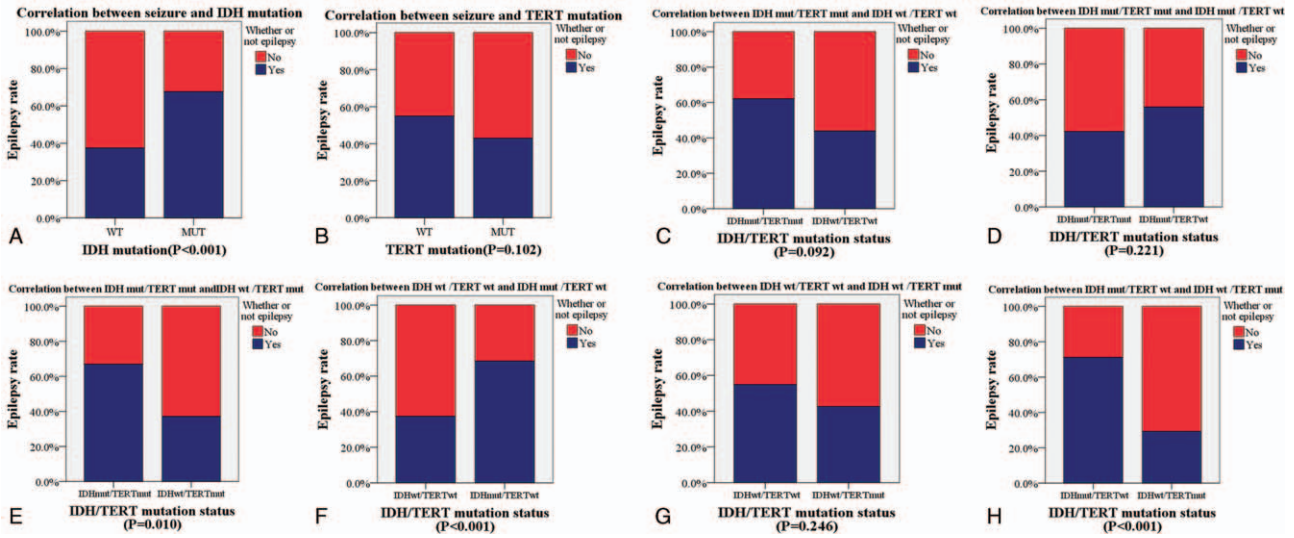

Figure 1. Correlation analysis between molecular pathology typing of IDH/*TERT*p and the incidence of tumor-related epilepsy. (A) Correlation analysis demonstrates epilepsy rate was significant higher in *IDH* mutation group than *IDH* wildtype group ($P < .001$, chi-square test).(B) Correlation analysis demonstrates that the epilepsy rate in the *TERT*p mutation group was not significantly correlated with the *TERT*p wildtype group ($P = .102$, chi-square test).(C) Correlation analysis demonstrates that the epilepsy rate in the *IDH* mut/*TERT*p mut group was not significantly correlated with the *IDH* wt/*TERT*p wt group ($P = .092$, chi-square test), (D) in the *IDH* mut/*TERT*p mut group was not significantly correlated with the *IDH* mut /*TERT*p wt group ($P = .221$, chi-square test).(E) Correlation analysis demonstrates epilepsy rate was significant higher in *IDH* mut/*TERT*p mut group than *IDH* wt/*TERT*p mut group ($P = .010$, chi-square test),(F) and in *IDH* mut /*TERT*p wt group than *IDH* wt/*TERT*p wt group ($P < .001$, chi-square test),(G) in the *IDH* wt/*TERT*p wt group was not significantly correlated with the *IDH* wt /*TERT*p mut group ($P = .246$, chi-square test). (H) Correlation analysis demonstrates epilepsy rate was significant higher in *IDH* mut/*TERT*p wt group than *IDH* wt/*TERT*p mut group ($P < .001$, chi-square test). *IDH* = isocitrate dehydrogenase, *TERT*p = telomerase reverse transcriptase promoter.

and tumor-associated seizures. The probability value of bilateral *P* values was .001 (Table 3), which was statistically significant.

On this basis, in order to further study whether the epilepsy is related to molecular pathological types of *IDH*/*TERT*p, we divided 289 subjects into 4 subgroups according to the *IDH*/*TERT*p mutations:[25]*IDH* mut/*TERT*p mut (n=44),*IDH* wt /*TERT*p wt (n=106),*IDH* mut /*TERT*p wt (n=55)and *IDH* wt /*TERT*p mut (n=84). We compare the frequency of epilepsy between the 4 groups based on *IDH*/*TERT*p mutations and conduct a chi-square test to analyze the potential impact of *IDH*/*TERT*p mutations on seizures (Supplementary Table 1, http://links.lww.com/MD/C700). The results showed that the incidence of epilepsy was highest in *IDH* mut/*TERT*p wt group (47.27%), followed by *IDH* mut/*TERT*p mut group (34.09%), the incidence of epilepsy is lower in *IDH* wt/*TERT*p wt group (19.81%) and *IDH* wt/*TERT*p mut group (13.10%). The correlation analysis revealed that there was statistical significance in seizure rates between *IDH* mut/*TERT*p mut group and *IDH* wt/*TERT*p mut group (Fig. 1**E**, $P = .010$, $X^2 = 7.864$, v = 1, chi-square test),in *IDH* wt/*TERT*p wt group and *IDH* mut/*TERT*p wt group (Fig. 1**F**, $P < .001$, $X^2 = 13.211$, v = 1,chi-square test), in *IDH* mut/*TERT*p wt group and *IDH* wt/*TERT*p mut group (Fig. 1**H**, $P < .001$, $X^2 = 19.876$, v = 1,chi-square test). However, there was no significant correlation in seizure rates between *IDH* mut/*TERT*p mut group and *IDH* wt/*TERT*p wt group (Fig. 1**C**, $P = .092$, $X^2 = 3.476$, v = 1, chi-square test), *IDH* mut/*TERT*p mut group and *IDH* mut /*TERT*p wt group (Fig. 1**D**, $P = .221$, $X^2 = 1.751$, v = 1,chi-square test),and *IDH* wt/*TERT*p wt group and *IDH* wt /*TERTp* mut group (Fig. 1**G**, $P = .246$, $X^2 = 1.509$, v = 1,chi-square test). These results further suggest that the *IDH* mutation may be one of the molecular pathological causes of preoperative seizures, whereas the *TERT*p mutation is not correlated with seizures.

Table 2

Correlation between seizure and *IDH*/*TERT*p mutations.

	IDH Status		*TERT*p Status	
	No mutation	mutation	No mutation	mutation
No Seizure	158	58	114	102
Seizure	32	41	47	26
Total	190	99	161	128
P value	**<.001**		.102	

IDH = isocitrate dehydrogenase, *TERT*p = telomerase reverse transcriptase promoter.

Table 3

Multivariate logistic regression analysis of the association between *IDH*/*TERT*p mutations and tumor-associated seizures.

				95% confidence interval for exp (B)	
Prognosis	Wald	Sig	Exp (B)	Lower bound	Upper bound
Histology	5.825	**0.016**	0.491	0.276	0.875
Location	1.038	0.308	0.667	0.305	1.455
IDH	10.986	**0.001**	2.637	1.486	4.677
TERT	0.169	0.681	0.886	0.498	1.577

IDH = isocitrate dehydrogenase, TERTp = telomerase reverse transcriptase promoter.

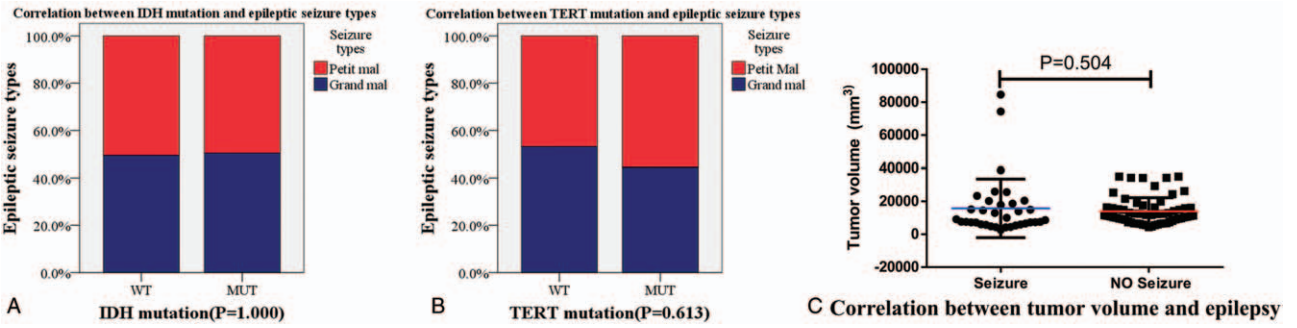

Figure 2. Correlation analysis between molecular pathological typing of IDH/*TERT*p and types of seizures. (A) Correlation analysis demonstrates that the seizure types was not significantly correlated with *IDH* mutations ($P=1.000$, chi-square test). (B) Correlation analysis demonstrates that the seizure types was not significantly correlated with *TERT* mutations ($P=.613$, chi-square test). (C) T-test results showed that there was no significant correlation between tumor volume and seizures ($P=.504$, *t* test). *IDH*=isocitrate dehydrogenase, *TERT*p=telomerase reverse transcriptase promoter.

3.3. Relationship between IDH/TERTp mutations and tumor-associated seizure types

Of the 289 patients included in this study, 73 had epileptic symptoms before surgery, of which 27 were partial seizures and 46 were general seizures. The correlation between *IDH* (Fig. 2**A**, $P=1.000$, $X^2=0.006$, v=1, chi-square test, Supplementary Table 2, http://links.lww.com/MD/C700) and *TERT*p (Fig. 2**B**, $P=.613$, $X^2=0.491$, v=1,chi-square test, Supplementary Table 2, http://links.lww.com/MD/C700) mutations and seizure types was analyzed. The results showed that in LGG patients, *IDH/TERT*p mutations did not have specific effects on the type of epileptic seizures. We collected the imaging data of 96 patients and calculated the tumor volume (tumor volume= length * width * height/2), and *t* test was used to investigate whether tumor volume was the influencing factor of tumor-related epilepsy. The results showed that there was no significant correlation between tumor volume and seizures (Fig. 2**C**, $P=.504$, *t* test).

4. Discussion

Gliomas are the most common malignancy in the CNS and one of the most common causes of tumor-related seizures. Sixty-five to ninety percent of patients with LGG have seizures as the initial symptom.[4,6] Patients with temporal, insular, and frontal gliomas are more prone to experience epilepsy, and LGG with oligodendroglial histology is closely related to preoperative seizures.[17] Many biomarkers are thought to be related to the onset of preoperative seizures. For a long time, researchers have been devoted to exploring biochemical changes in the tumor microenvironment and searching for mechanisms and influencing factors of tumor-associated seizures at the level of molecular biology.[5,7,8] Tumor suppressor gene *LGI1* was found associated with epilepsy in patients with LGG.[34] High-mobility group box 1 (HMGB1) is an endogenous danger signal, and it evokes inflammatory reactions by activating various immune-related cells when released extracellularly, which includes microglia in the case of the brain.[35] In particular, HMGB1 is induced and released by dying or activated immune cells in epileptic tissues, and contributes to the etiopathogenesis of seizure by increasing neuronal excitability.[38] However, the relationship between the *IDH* mutation and glioma-related epilepsy has only begun to be studied in recent years. The relationship between *TERT*p mutations and seizures is by far not explored. In this study, we retrospectively analyzed the clinical and molecular pathologic data of 289 low-grade glioma patients to investigate whether the *IDH/TERT*p mutations are associated with preoperative seizures and types of seizures.

According to previously reported studies, glioma-associated epilepsy often occurs in patients with LGG.[18] The cause of epilepsy may be multi-factor and complex, and it is still poorly understood.[19] There is evidence that elevated glutamate concentrations in gliomas and changes in glutamate transporter expression are associated with the onset of tumor-associated epilepsy and may play an important role in its pathogenesis.[13] Histological types and WHO ratings also seem to strongly correlated with seizures occurrence.[20] There are many other strong risk factors for preoperative seizures that have been highlighted in previous research, including high levels of adenosine kinase and low levels of gamma-aminobutryic acid.[22,23] However, perhaps the different rates of epilepsy are explained not only by tumoral or peritumoral microenvironment changes, and the internal relationship of genetic factors of the tumor or the peritumoral brain tissue may be part of the reason for these seizures.[24]

In this study, we demonstrated that *IDH* mutation is a significant factor influencing the occurrence of tumor-related seizures which is in line with the previous studies.[4,32] On this basis, we also investigated the effect of *TERT* mutation on preoperative seizures, and revealed no significant correlation between *TERT*p mutations and seizure in LGG patients. We also explored the correlation between the *IDH/TERT*p mutations and seizure types and further study the relationship between *IDH/TERT*p mutations and types of seizures at the molecular level to get a more comprehensive and objective conclusion.

The mutated *IDH* reduces ketoglutarate to 2-hydroxyvalerate (2Hg) instead of converting isocitrate to ketoglutarate. This led to a 100-fold increase in 2Hg levels in *IDH*-mutant gliomas.[11,21] Linninger, et al found that in the low millimolar range, a relatively large D2HG concentration may be present in and around the glioma in which the IDH1 mutation occurs.[33] 2Hg is similar to the glutamine structure and can activate N-methyl-D-aspartate (NMDA) receptors, suggesting that 2Hg may play a potential role in the development of epilepsy.[12,13] Chen, et al's research obtained similar conclusions, the D2HG product of the mutated IDH1 may increase neuronal activity by mimicking glutamate activity on the NMDA receptor, and glioma patients

with IDH1 mutations are more likely to develop seizures.[32] These findings have important implications for personalized treatment of tumor-associated epilepsy.[32]

*TERT*p is another molecular marker of glioma discovered in recent years, and the total mutation rate is about 50%.[14] Recent studies have found that mutations in the *TERT*p are common in gliomas and that *TERT*p promoter mutations may be promising biomarkers in glioma survival prognostication when combined with *IDH* mutations.[25]*TERT*p promoter mutations often occur in all types of gliomas, suggesting that telomerase-regulated telomere extension may play an important role in the pathogenesis of gliomas.[26,27,28] The *TERT*p gene encodes a telomerase catalytic subunit, which is an enzyme that elongates telomeres in cells and prevents the degradation of multiple mitotic chromosomes.[29,30] Mutations in the *TERT*p promoter region most commonly occur in C228 T and C250T. This mutation can increase the activity of the *TERT*p promoter[14] and provide a new binding site for E-twenty-six (ETS).[31] Although studies on *TERT*p mutations and gliomas in etiology and prognosis have seen initial successes in recent years, studies on the potential link between *TERT*p mutations and tumor-related seizures have been lacking. In the present study, we first explored the effect of *TERT*p mutations on preoperative epilepsy in LGG patients but revealed no definite correlation between the 2. This finding reinforced the dominating position of *IDH* mutations in the initiation of seizures in LGG patients.

However, this study has some limitations. First, our analysis was based on retrospective data. Second, our sample is not large enough, especially when patients are divided into different subgroups, the sample is relatively limited. Finally, the specific mechanism of *IDH* mutation affecting epilepsy remains to be further studied and demonstrated.

To sum up, in patients with LGG with epileptic seizures as the initial symptom, *IDH* mutations are more common, suggesting that this genotype is positively correlated with preoperative seizures. However, there was no significant correlation between *TERT*p mutations and seizures. *IDH/TERT*p mutations have no definite effect on the type of epileptic seizures in patients with LGG.

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