Molecular characteristics of long-term epilepsy-associated tumours (LEATs) and mechanisms for tumour-related epilepsy (TRE)

Thomas J Stone¹,²
Rachel Rowell³,⁴
Bodiabaduge Ashan Prasanna Jayasekera³,⁴
Mark O Cunningham³,⁴
Thomas S Jacques¹,²

¹ Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health, London, WC1N 1EH, UK
² Department of Histopathology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH, UK
³ Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK
⁴ Department of Neurosurgery, Royal Victoria Hospital, Newcastle upon Tyne, NE1 4LP, UK

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Abstract

Brain tumours are the second most common cause of seizures identified in epilepsy surgical series. While any tumour involving the brain has the potential to cause seizures, specific subtypes are more frequently associated with epilepsy. Tumour-related epilepsy has a profound impact on patients with brain tumours and these seizures are often refractory to anti-epileptic treatments, resulting in long-term disability and patient morbidity. Despite the drastic impact epilepsy-associated tumours have on patients, they have not traditionally enjoyed as much attention as more malignant neoplasms. However, recently a number of developments have been achieved towards furthering our understanding of the molecular and developmental backgrounds of specific epilepsy associated tumours. In addition, the past decade has seen an expansion in the literature on the pathophysiology of tumour-related epilepsy. In this review, we aim to summarise the mechanisms by which tumours may cause seizures and detail recent data regarding the pathogenesis of specific developmental epilepsy-associated tumours.

Introduction

Epilepsy is a common symptom among patients with brain tumours. Moreover, tumour-related epilepsy (TRE) has a profound impact on patient quality of life and frequently results in severe long-term disability. Any tumour affecting the brain has the potential to cause seizures, and in surgical series of patients with long-term epilepsy brain tumours are the second most common cause after focal cortical dysplasia in children and hippocampal sclerosis in adults [1].
Within the spectrum of brain tumours, specific types are more frequently associated with seizures [2]. The most common brain tumours in epilepsy surgical series are usually glioneuronal tumours, often dysembryoplastic neuroepithelial tumours (DNET) or gangliogliomas. These lesions fall within a group often called long-term epilepsy-associated tumours (LEATs), a category of tumours characterised by long histories of refractory epilepsy [3].

In this review, we will address two crucial questions with regards to tumour-related epilepsy. In the first part, we will explore the general mechanisms by which any type of tumour can cause seizures. In the second part, we will explore recent developments in the pathogenesis of developmental glioneuronal tumours/LEATs.

Mechanisms for tumour associated epilepsy

The past decade has seen an expansion in the literature regarding the pathophysiology of tumour-related epilepsy (TRE). Broadly, two hypotheses have been proposed; the tumouricentric hypothesis and the epileptogenic hypothesis (Figure 1). The former suggests epileptogenicity is derived from the tumour itself, while the latter argues epileptogenicity derives from the peri-tumoural tissue [4-6]. In either case multiple mechanisms are likely to underpin tumour-associated epileptogenesis. The following sections aim to consolidate the current understanding of TRE and explore potential developments.

Disruption of glutamate homeostasis

Disruption of glutamate metabolism in the tumour and surrounding tissue promotes neural toxicity, tumour growth, and epileptogenesis [7,8]. The latter is reflected by a greater rate of seizure recurrence following tumour resection in patients with higher peri-tumoural glutamate [9]. SLC7A11 encodes a cystine/glutamate antiporter, system XC (SXC), which is responsible for extracellular glutamate release in exchange for cystine uptake [10]. Interestingly, SLC7A11 expression is correlated with seizures in both human and animal tumour models, and is up-regulated in gliomas [7,11-13]. Robert et al. reported that in mice, peri-tumoural neurons adjacent to SLC7A11 expressing gliomas had depolarised resting potentials and fired more action potentials versus SLC7A11 negative gliomas, demonstrating a hyper-excitable state in the former [13]. Moreover, the
authors reported that mice xenografted with SLC7A11 expressing gliomas experienced significantly more seizures (70-77%) than those with SLC7A11 negative gliomas (1%).

SXC is present in both neurons and glial cells, and is up-regulated in response to ischaemia, oxidative stress, and trauma – all of which are mediated by tumour growth. In addition to its implications for hyper-excitability, glutamate contributes to excitotoxicity and neuronal cell death, allowing for tumour growth (Figure 2) [10,11]. Additionally, cystine is an important precursor for the production of glutathione, which may confer a protective advantage under conditions of ischaemia and oxidative stress which may occur within the tumour. This may be reflected in reduced survival time for patients whose tumours display SLC7A11 expression [13].

Glutamate homeostasis may also be disrupted through changes in the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), a glutamate receptor. Such changes have been reported in gliomas and may promote increased excitability and epileptogenicity [14]. AMPA receptors are composed of 4 subunits, one of which – GluA2 – is often post-translationally modified, rendering the receptor impermeable to calcium [15,16]. AMPA receptors lacking this modification, and therefore permeable to calcium, are implicated in a number of neurodegenerative diseases including epilepsy [17]. Illustrating this, one study found that mice lacking modified GluA2 developed early seizures and died prematurely [18]. Alterations in ADAR2, the enzyme responsible for GluA2 modification, is observed in some epilepsy-associated tumours [19]. Additionally, down-regulation of ADAR2 is reported in gliomas, and results in an increase in calcium permeable receptors (Figure 3) [20]. Elevated intracellular calcium has a number of effects, including phosphorylation of AMPA receptors and increased trafficking of AMPA receptors to the cell membrane. The former increases glutamate sensitivity while the latter increases excitability. In addition, studies suggest that ischaemia - a possible result of tumour growth - also drives AMPA receptor trafficking to the postsynaptic membrane, further compounding this mechanism of hyper-excitability [17,21,22].

Alterations in ions and ion channels

Disrupted chloride homeostasis is reported in a number of epilepsy disorders, including TRE [23-27]. In particular, the potassium chloride co-transporter, KCC2, is implicated [28]. KCC2 enables extracellular potassium and chloride release, and is essential for maintaining a chloride gradient

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across neurons. Moreover, KCC2 is important in regulating GABA function by altering intracellular chloride levels to alternate between hyperpolarising and depolarising GABAergic signalling. KCC2 expression alterations are reported in gliomas, and down-regulation is reported in the peri-tumoural tissue of mouse glioma models, corresponding with spontaneous seizures [28-30]. Similarly, down-regulation of KCC2 is observed in peri-tumoural epileptic cortex [31]. Taken together, these studies imply reduced KCC2 expression, resulting in increased intracellular chloride, may impair inhibitory GABA activity and result in increased excitability and a reduced seizure threshold. Notably, down-regulation of KCC2 may occur in response to elevated glutamate, and as such this mechanism may interact with and be compounded by disrupted glutamate homeostasis [28,32].

Another chloride transporter implicated in epileptogenesis is NKCC1. NKCC1 is up-regulated in human glioma and drives increases in intracellular chloride [23]. Up-regulation of NKCC1 is reported in ganglioglioma, a tumour almost always associated with seizures, and coincides with down-regulation of KCC2 [29,33]. Moreover, treatment with bumetanide, an NKCC1 antagonist, reduces seizure frequency in patients with temporal lobe epilepsy [34]. Taken together, these data suggest NKCC1 as a potential therapeutic target for TRE, and warrants further investigation of its role in TRE [35]. Additional molecules involved in ion transport and implied to play a role in epileptogenesis include aquaporin-4 and Kir4.1. Aquaporin-4 is reported to be over-expressed in glioblastoma patients presenting with seizures, while mutations in Kir4.1 are associated with epilepsy in humans and mouse models [36,37].

Alterations of the blood brain barrier

Brain tumours frequently disrupt the blood brain barrier (BBB), and there is evidence to suggest an epileptogenic effect. For example, Marchi et al. demonstrated that acute disruption of the BBB after administration of mannitol resulted in seizures [38]. The degree of seizure activity correlated with the degree of disruption. Interestingly, electrographic seizure activity also appeared in the opposite hemisphere to that which had experienced BBB disruption, and the authors suggested a spatial relationship between epileptogenic foci and the location of BBB disruption. This is particularly relevant for TRE, in which the lesion and epileptogenic foci are often in distinct locations. A number of studies have similarly suggested a causal relationship between BBB disruption and seizures, and support for an association between impaired BBB function, increased neuronal excitability, and

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seizures is suggested by Alexander disease [39-41]. In this condition, a feature of which is seizures, mutations affecting GFAP cause a delay in BBB development [42,43].

At a cellular level, impaired BBB function alters pH homeostasis, allows leakage of large molecules like albumin and glutamate, causes oedema, and can modulate expression of ion channels [44]. pH changes in the form of increasing alkalinity can increase neuronal excitability [45]. This can also result from modulation of astrocyte function by albumin via TGF-β [44]. Interestingly, the glutamate antiporter SXC, detailed previously, is also implicated in BBB disruption. Rats with SXC knock down gliomas possess significantly less peri-tumoural oedema than those with high SXC expression, suggesting SXC may contribute to BBB disruption [46].

**Alterations in intercellular connections**

Amplified intercellular coupling as a result of increased gap junction expression is thought to play a role in the synchronisation of discharges from epileptogenic foci [47]. For example, increased expression of the gap junction protein connexin 43 (Cx43) is observed in human epileptic disorders, and in the peri-tumoural tissue of glioma patients with seizures [47-50]. Interestingly, increased Cx43 expression has also been observed in low-grade versus high-grade glioma, and may contribute towards the increased seizure occurrence in the former [49-51]. Despite these associations, the role of gap junctions in epileptogenesis is unclear. Increased cellular connectivity is suggested to allow for increased excitability, but is also observed to result in decreased excitability through increased buffering of potassium and glutamate (Figure 4). Additionally, reduced intercellular coupling may generate hyper-excitability through reduced buffering of ions and amino acids [52]. A number of other gap junctions are implicated in TRE, including oligodendroglial, neuronal, and additional astrocytic connexins. However, there is no formal consensus on the mechanisms by which alterations in these junctions exert excitatory or inhibitory effects, and whether such alterations represent a causal or consequential relationship with seizures.

**Alterations in brain networks**

Brain tumours disrupt local and distal cortical networks, increasing vulnerability to seizures. Magnetoencephalography studies have shown that glioma patients display perturbed functional
connectivity with effects on the architecture of small world networks, intrahemispheric neuronal communication, local/distal network connectivity, and neuronal communication in distal areas [53,54]. These factors may explain why epileptogenic foci are often found at sites remote to the tumour.

Differences between the connectomic profiles and default mode networks in low- and high-grade gliomas have been observed, with low-grade gliomas displayed higher connectivity indices than their high-grade counterparts [55]. This led to suggestion that the slow-growing nature of low-grade tumours allows for the establishment of greater connectivity, thus increasing seizure vulnerability. If validated, this may help explain the higher incidence of seizures seen in low-grade tumours. Increases in default mode networks have also been observed in low-grade gliomas located in the hippocampal and prefrontal regions. Interestingly, in low-grade tumours these networks were lateralised to the opposing hemisphere to the tumour, a feature that was not seen in high-grade glioma [56]. However, a relationship between the alteration of default mode networks and seizure frequency has yet to be established.

**Inflammation**

Inflammation and immune responses in the brain have the potential to contribute towards epileptogenesis via a number of routes. These include astrocyte dysfunction, vascular permeability, and disruption of the blood brain barrier [57,58]. Genetic studies have demonstrated that there is a significant increase in expression of inflammatory mediators within brain tumours and surrounding tissues [12,33]. These include inflammatory cytokines, such as TNF-a, and prostaglandins, which can stimulate the calcium dependent release of glutamate from astrocytes [59]. Additional inflammatory molecules and pathways implicated in epileptogenesis include toll like receptors, TGF-B, cyclooxygenase, the complement pathway, and pathways involving IL-1 [57]. Interestingly, gliomas possess the capacity to up-regulate IL1 [60]. However, despite these associations, further work is necessary to explore the potential for a causal relationship between inflammatory mediators and seizure occurrence.
Molecular biology of long-term epilepsy-associated tumours

In the following sections, we will turn to recent developments in specific epilepsy-associated tumours (i.e. LEATs), in particular developments in the molecular biology of these tumours. We will focus primarily on rarer and newly described entities. LEATs are the second most common pathology identified in epilepsy surgical series [1]. Unlike more malignant tumours, these are important not because of the potential for progression or recurrence but due to the devastating impact of drug-resistant epilepsy that is associated with them, leading to significant long-term disability and poor development outcomes for affected children. In spite of this massive impact, these tumours are relatively poorly understood, however a number of recent studies have highlighted important molecular features that grant insights into the development of these tumours. In addition, a handful of novel, often rare, tumour types have been characterised in recent years.

The ganglioglioma and dysembryoplastic neuroepithelial tumour spectrum

Ganglioglioma and dysembryoplastic neuroepithelial tumour are the most frequently identified tumours in epilepsy surgical series, yet their molecular backgrounds are poorly understood [2]. A particular problem associated with these tumours is a lack of clarity regarding classification. The histological classification of ganglioglioma and DNET are poorly reproducible, and this is illustrated by a sizeable variance in reported frequencies across surgical series (reviewed in [61]).

*BRAF*-V600E and *FGFR1* mutations are common in ganglioglioma/DNET. However, the reported frequencies of the former vary significantly across surgical series (Table 1) [62] [63-71]. For example, two large studies of 77 and 71 ganglioglioma identified *BRAF*-V600E in 14 (18%) and 41 (58%) of tumours, respectively [63,64]. Mirroring this, two studies of 20 and 51 DNETs identified *BRAF*-V600E in 6 (30%) and 26 (51%) tumours, respectively [69,70]. These widely variable frequencies suggest that the underlying biology of these two tumours may not be well captured by traditional histological classification. More recently, a number of studies have suggested that DNET can be distinguished by the presence of *FGFR1* mutations, most commonly a tyrosine kinase domain duplication. Qaddoumi et al. observed *FGFR1* mutations in 18/22 (82%) DNETs – 9 tyrosine kinase domain duplications, 8 missense SNVs, and 1 *FGFR1-TACC1* fusion – but also noted that similar mutations were common to diffuse low-grade tumours with an oligodendroglial phenotype [65]. This result was replicated by Rivera et al., who identified *FGFR1* mutations in 25/43 (58%) of DNET.
These were tyrosine kinase domain duplications in 12, point mutations in 10, and breakpoints in 3 tumours respectively [71].

The variable mutation frequencies described in the literature and poorly reproducible histological classification raises the question how many distinct tumour entities exist within the ganglioglioma/DNET spectrum, and how can we identify them? To address this, we recently undertook a study to investigate the number of tumour types within the ganglioglioma/DNET spectrum and elucidate their underlying biology [72]. To this end, we employed a class discovery approach to classify tumours. In such an approach, the genomic data is used in an unsupervised manner to identify how many distinct biological groups of tumours are present. As a result, tumours are grouped according to biological similarity rather than histological appearance. Interestingly, we noted that glioneuronal tumours fell into two groups which were only partially concordant with histology. The first of these (Group 1) was skewed in favour of tumours with the histological features of ganglioglioma, while the second (Group 2) favoured DNET-like histology. However, both contained ganglioglioma, DNET, and a third category of tumours with mixed histological features which were evenly distributed between groups. Group 1 tumours were enriched for \( \text{BRAF-V600E} \) mutations, which were absent in Group 2 tumours. In contrast, Group 2 tumours were enriched for \( \text{FGFR1} \) mutations. Notably, when we analysed RNA expression data from each of the two groups, we identified enrichments for astrocyte associated genes in Group 1 and oligodendrocyte precursor associated genes in Group 2 tumours, potentially indicating distinct developmental processes for each of these tumours. While further studies will be necessary to validate these findings, these data highlight the unreliable nature of histological classification in isolation for these tumours. However, the \( \text{BRAF} \) and \( \text{FGFR1} \) mutations are not specific to this spectrum of tumours (see below). This suggests that the diagnostic approach needs to integrates the histological, mutational and genomic profiling data in order to distinguish these tumours from one another and from other tumours with similar mutations.

**Rare and recently defined LEAT subtypes**

In recent years, a number of advances have been attained in our understanding of the molecular biology of rare LEAT subtypes. In addition, a handful of novel tumour types have been proposed, identified by conventional histological examination and molecular profiling. In the following passages, we will explore these tumours and the studies pertaining to them.
Angiocentric glioma

Angiocentric glioma is a rare tumour recognised as a distinct entity in the 2007 WHO classification [73]. Until recently, the molecular genetic landscape of angiocentric glioma remained relatively unexplored, with only one study able to identify infrequent abnormalities [74]. However, in 2016 Qaddoumi et al. were able to identify recurrent MYB alterations in all angiocentric glioma assayed [65]. 13/15 (87%) of these possessed a MYB-QKI fusion, with the remaining two possessing a MYB-ESR1 fusion and QKI rearrangement, respectively. The prevalence of MYB alterations in angiocentric glioma was repeated in a subsequent cohort of 19 tumours, all of which were found to harbour MYB-QKI fusions [75]. This study also demonstrated that MYB-QKI fusion was able to drive tumorigenesis via simultaneous activation of MYB, as a result of enhancer translocation, combined with loss of the tumour suppressor activity of QKI. Taken together, these data suggest that MYB abnormalities are sufficient as a specific and single driver event in angiocentric glioma.

Multinodular and vacuolating neuronal tumours (MVNT)

Multinodular and vacuolating neuronal tumours are a rare neoplasm first described in 2013 [76]. At the time of writing, descriptions of only 27 MVNT are available in the literature [76-83]. These tumours are identified by a distinctive nodular pattern of neuronal tumour cells with vacuolation, but may otherwise resemble ganglioglioma/gangliocytoma. Across all reports, a total of 17 cases have been investigated for the presence of BRAF-V600E, which was absent in all [76,77,80,81]. Additionally, in a recent series of 10 cases, no mutations in FGFR1 or MYB could be identified [77]. Given the prevalence of mutations affecting BRAF, FGFR1, and MYB in other LEATs, the absence of these mutations in MVNT may be useful in distinguishing these tumours. Thus far, only a handful of molecular abnormalities have been positively identified in MVNT. The first of these was a MAP2K1-Q56P mutation in one case from the original cohort of 10 [76]. More recently, recurrent synonymous SNPs were identified in DEPDC5, SMO, and TP53 for all MVNT tested in a separate cohort of 10 tumours [77]. Within this cohort the authors also identified an NPRL3 variant in 5/8 tumours tested and non-recurrent SNPs across the cohort affecting SUFU, EZH2, CIC, and PIK3CA. While these data provide a useful glimpse of the molecular background of MVNT, further molecular genetic investigation of these tumours is necessary to elucidate recurrent features in their underlying biology. However, as these are rare tumours that have only recently been described, the
large cohort studies necessary to resolve these questions may only be possible through the retrospective review and reclassification of archival cohorts from multiple specialist centres.

**Polymorphous low-grade neuroepithelial tumour of the young (PLNTY)**

Polymorphous low-grade neuroepithelial tumours of the young are another recently described entity, with only a single study describing these entities at the time of writing [84]. Of the 10 tumours reported by Huse et al., 8 underwent molecular analyses, of which 7 found to harbour a mutation. These corresponded to 3 \( \text{BRAF-V600E} \) mutations, 3 \( \text{FGFR2} \) fusions (2x \( \text{KIAA1598} \), 1x \( \text{CTNNA3} \)), and 1 \( \text{FGFR3-TACC3} \) fusion. These tumours are proposed to represent a high proportion of low-grade oligodendrogial tumours in children, and are distinguished from other low-grade tumours by a distinct DNA methylation profile. As with MVNT, further studies are necessary to robustly characterise PLNTY, and a retrospective review of archival tumours, particularly those with low-grade oligodendrogial morphologies may identify a number of these tumours for the further investigation in larger cohorts.

**Isomorphic astrocytoma**

Isomorphic astrocytoma are a subtype of diffuse astrocytoma proposed in 2004 by Blümcke et al. but not yet officially recognised by the WHO [85]. These astrocytoma variants are characterized by a low cellularity and consist of highly differentiated astroglial cells with small, round nuclei and finely branching processes. Additionally, a homogenous fibrillary tumour matrix is present. These tumours also show excellent progression-free survival. In the original series, all 6 patients were alive at follow up (up to 13 years). A second study describing 7 isomorphic astrocytoma reiterated the positive outlook for patients with this subtype, noting 50% fewer recurrences in these patients compared to those with conventional diffuse astrocytoma [86]. In addition, this variant seems to arise in younger patients than conventional diffuse astrocytoma, with a mean age at onset of 14.4 years across 29 cases collected by the European Epilepsy Brain Bank [2]. Thus far, no specific molecular features have been identified for isomorphic astrocytoma, and so further studies are necessary to investigate the molecular background of this LEAT.
Common and well-defined epilepsy-associated tumours

We have focussed on the more contentious and novel entities in LEATS. However, a range of other more common tumours can present with long term epilepsy. In the context of tumours developing early in life and presenting with epilepsy, two common entities are pilocytic astrocytoma (PA) and pleomorphic xanthoastrocytoma (PXA). These tumours predominantly harbour abnormalities of the MAP kinase pathway, frequently BRAF abnormalities. In pilocytic astrocytomas, the most common abnormality is a BRAF-KIAA1549 fusion, although a proportion of cases may possess BRAF-V600E mutations [63,87,88]. Other mutations observed infrequently in PA include those affecting NF1, KRAS, the NTRK family, and FGFR1 [89,90]. In PXA, 60-78% of cases possess BRAF-V600E mutations [63,69,90-93]. Additionally, a large proportion of PXA may harbour deletions involving CDKN2A, ARF, and CDKN2B loci [94].

Summary

The limited efficacy of empirical treatments for tumour-related epilepsy reflects an incomplete understanding of the underlying pathophysiology. However, growing evidence from animal models, analyses of patient tissue, and sophisticated imaging in the form of magnetic resonance spectroscopy and magnetoencephalography are helping to shed light on the disparate mechanisms that contribute towards the generation of seizures in patients with CNS tumours. Concurrently, advances in molecular biology are generating novel insights into the biology of these tumours, allowing us to segregate and classify novel biologically meaningful entities. Improvements in our understanding of the development of these tumours and the mechanisms by which they inflict seizures will allow for the improvement of patient quality of life through novel treatments and management strategies. An example of this is the recent promise displayed by the AMPA receptor antagonist, perampanel, for the reduction of seizure frequency in glioma patients with refractory seizures [95]. Similarly, bumetanide, an NKCC1 antagonist, has been shown to reduce seizure frequency in patients with temporal lobe epilepsy [34]. A final example is the treatment of BRAF-V600E positive LEATs with dabrafenib [96]. Future work should aim to disentangle the putative mechanisms of TRE, deepen the knowledge base surrounding the molecular aspects of epilepsy-associated tumours, and potentially relate the two to one another.
Figure & Table Legends

Figure 1: Changes in the tumour and peri-tumoural tissue may mediate seizures. The tumouricentric hypothesis suggests that seizures are a direct consequence of the tumour. The epileptogenic hypothesis suggests that seizures are the result of changes within the peri-tumoural tissue.

Figure 2: Glioma cells release glutamate, contributing to neuronal cell death and facilitating tumour growth. Concurrently, these cells take up cystine, which may confer a survival advantage under ischaemic conditions. This exchange is mediated by system XC (SXC), a cystine/glutamate antiporter.

Figure 3: Down-regulation of ADAR2, which post-translationally modifies GluA2, results in the formation of calcium permeable AMPA receptors. Elevated intracellular calcium increases AMPA receptor phosphorylation and trafficking to the membrane, thereby increasing glutamate sensitivity and excitability.

Figure 4: Increased expression of connexin 43 may permit neuronal synchronisation, thus increasing excitability (A). However, it may also reduce excitability by buffering glutamate and potassium between cells (B).

Figure 5: The histological appearances of rare types of LEAT. (A) shows vacuolated neurons from a multinodular and vacuolating neuronal tumour (MVNT). (B) shows the pattern of an isomorphic astrocytoma with bland glial nuclei set against a fibrillary stroma. (C) and (D) shows the perivascular arrangements of tumour cells in an angiocentric glioma. Scale bars A, B, D-50μm, C-100μm

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Table 1: The reported incidence of BRAF-V600E mutations in ganglioglioma and DNET is widely variable across individual series.

Table 2: Pathogenic mutations reported in long-term epilepsy-associated tumours. Group 1 and Group 2 glioneuronal tumours are as defined in Stone et al. [72].

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### Ganglioglioma

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### DNET

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### Tumour

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Peritumoural tissue:
- Disrupted glutamate homeostasis
- Alterations in ion channels
- Alterations in the blood brain barrier
- Alterations in intercellular connections
- Alterations in brain networks
- Inflammation

Tumour:
- Disrupted glutamate homeostasis
- Alterations in the blood brain barrier
- Inflammation