DR THOMAS S JACQUES (Orcid ID : 0000-0002-7833-2158)

Article type : Annual Review Issue - Review

**Mail id:** t.jacques@ucl.ac.uk

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

Thomas J Stone[1,2]

Rachel Rowell[3,4]

Bodiabaduge Ashan Prasanna Jayasekera[3,4]

Mark O Cunningham[3,4]

Thomas S Jacques[1,2]

[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

**Keywords: LEAT, Epilepsy, Glioneuronal tumour, Ganglioglioma, Dysembryoplastic neuroepithelial tumour**

**Acknowledgements:**

We are grateful for funding from the Brain Tumour Charity, Great Ormond Street Children's Charity, Children with Cancer UK, the Olivia Hodson Cancer Fund and the National Institute for Health

Research. This report is independent research supported by the National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

**Author Contributions:**

All authors contributed to writing and editing the manuscript.

**Ethical Approval:**

Not applicable

**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

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

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 *BRAF*-V600E mutations, which were absent in Group 2 tumours. In contrast, Group 2 tumours were enriched for *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 *BRAF* and *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 *BRAF*-V600E mutations, 3 *FGFR2* fusions (2x *KIAA1598*, 1x *CTNNA3*), and 1 *FGFR3-TACC3* fusion. These tumours are proposed to represent a high proportion of low-grade oligodendroglial 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 oligodendroglial 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

**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].

**References**


1. Blümcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, Pfäfflin M, Elger C, Widman G, Schramm J, Becker A, Braun KP, Leijten F, Baayen JC, Aronica E, Chassoux F, Hamer H, Stefan H, Rössler K, Thom M, Walker MC, Sisodiya SM, Duncan JS, McEvoy AW, Pieper T, Holthausen H, Kudernatsch M, Meencke HJ, Kahane P, Schulze-Bonhage A, Zentner J, Heiland DH, Urbach H, Steinhoff BJ, Bast T, Tassi L, Russo Lo G, Özkara Ç, Oz B, Krsek P, Vogelgesang S, Runge U, Lerche H, Weber Y, Honavar M, Pimentel J, Arzimanoglou A, Ulate-Campos A, Noachtar S, Hartl E, Schijns O, Guerrini R, Barba C, Jacques TS, Cross JH, Feucht M, Mühlebner A, Grunwald T, Trinka E, Winkler PA, Gil-Nagel A, Toledano Delgado R, Mayer T, Lutz M, Zountsas B, Garganis K, Rosenow F, Hermsen A, Oertzen von TJ, Diepgen TL, Avanzini G, EEBB Consortium. Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery. N Engl J Med. 2017; 377(17): 1648–56.

2. Blümcke I, Aronica E, Urbach H, Alexopoulos A, Gonzalez-Martinez JA. A neuropathology-based approach to epilepsy surgery in brain tumors and proposal for a new terminology use for long-term epilepsy-associated brain tumors. Acta Neuropathol. 2014; 128(1): 39–54.

3. Luyken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, Schramm J. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia.; 44(6): 822–30.

4. Cowie CJA, Cunningham MO. Peritumoral epilepsy: Relating form and function for surgical success. Epilepsy & Behavior. 2014; 38(C): 53–61.

5. van Breemen MSM, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007; 6(5): 421–30.

6. Pallud J, Audureau E, Blonski M, Sanai N, Bauchet L, Fontaine D, Mandonnet E, Dezamis E, Psimaras D, Guyotat J, Peruzzi P, Page P, Gal B, Párraga E, Baron M-H, Vlaicu M, Guillevin R, Devaux B, Duffau H, Taillandier L, Capelle L, Huberfeld G. Epileptic seizures in diffuse low-grade gliomas in adults. Brain. 2013; 137(2): 449–62.

7. Yuen TI, Morokoff AP, Bjorksten A, D'Abaco G, Paradiso L, Finch S, Wong D, Reid CA, Powell KL, Drummond KJ, Rosenthal MA, Kaye AH, O'Brien TJ. Glutamate is

associated with a higher risk of seizures in patients with gliomas. Neurology. 2012; 79(9): 883–9.

8. Ye ZC, Sontheimer H. Glioma cells release excitotoxic concentrations of glutamate. Cancer Res. 1999; 59(17): 4383–91.

9. Neal A, Yuen T, Bjorksten AR, Kwan P, O'Brien TJ, Morokoff A. Peritumoural glutamate correlates with post-operative seizures in supratentorial gliomas. J Neurooncol. 2016; 129(2): 259–67.

10. Bridges RJ, Natale NR, Patel SA. System xc- cystine/glutamate antiporter: an update on molecular pharmacology and roles within the CNS. British Journal of Pharmacology. 2011; 165(1): 20–34.

11. Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA-K, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist P-H, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, Feilitzen von K, Forsberg M, Persson L, Johansson F, Zwahlen M, Heijne von G, Nielsen J, Pontén F. Proteomics. Tissue-based map of the human proteome. Science. 2015; 347(6220): 1260419.

12. Zhou X-W, Wang X, Yang Y, Luo J-W, Dong H, Liu Y-H, Mao Q. Biomarkers related with seizure risk in glioma patients: A systematic review. Clin Neurol Neurosurg. 2016; 151: 113–9.

13. Robert SM, Buckingham SC, Campbell SL, Robel S, Holt KT, Ogunrinu-Babarinde T, Warren PP, White DM, Reid MA, Eschbacher JM, Berens ME, Lahti AC, Nabors LB, Sontheimer H. SLC7A11 expression is associated with seizures and predicts poor survival in patients with malignant glioma. Sci Transl Med. 2015; 7(289): 289ra86.

14. Aronica E, Yankaya B, Jansen GH, Leenstra S, van Veelen CW, Gorter JA, Troost D. Ionotropic and metabotropic glutamate receptor protein expression in glioneuronal tumours from patients with intractable epilepsy. Neuropathology and Applied Neurobiology. 2001; 27(3): 223–37.

15. Gouaux E. Structure and function of AMPA receptors. The Journal of Physiology. 2004; 554(2): 249–53.

16. Jacob AL, Weinberg RJ. The organization of AMPA receptor subunits at the postsynaptic membrane. Hippocampus. 2015; 25(7): 798–812.

17. Wright A, Vissel B. The essential role of AMPA receptor GluR2 subunit RNA editing in the normal and diseased brain. Front Mol Neurosci. 2012; 5: 34.

18. Brusa R, Zimmermann F, Koh DS, Feldmeyer D, Gass P, Seeburg PH, Sprengel R. Early-onset epilepsy and postnatal lethality associated with an editing-deficient GluR-B allele in mice. Science. 1995; 270(5242): 1677–80.

19. Kitaura H, Sonoda M, Teramoto S, Shirozu H, Shimizu H, Kimura T, Masuda H, Ito Y,

Takahashi H, Kwak S, Kameyama S, Kakita A. Ca 2+-permeable AMPA receptors associated with epileptogenesis of hypothalamic hamartoma. Epilepsia. 2017; 58(4): e59–e63.

20. Maas S, Patt S, Schrey M, Rich A. Underediting of glutamate receptor GluR-B mRNA in malignant gliomas. Proc Natl Acad Sci USA. 2001; 98(25): 14687–92.

21. Liu B, Liao M, Mielke JG, Ning K, Chen Y, Li L, El-Hayek YH, Gomez E, Zukin RS, Fehlings MG, Wan Q. Ischemic insults direct glutamate receptor subunit 2-lacking AMPA receptors to synaptic sites. J Neurosci. 2006; 26(20): 5309–19.

22. Pellegrini-Giampietro DE, Zukin RS, Bennett MV, Cho S, Pulsinelli WA. Switch in glutamate receptor subunit gene expression in CA1 subfield of hippocampus following global ischemia in rats. Proc Natl Acad Sci USA. 1992; 89(21): 10499–503.

23. Pallud J, Le Van Quyen M, Bielle F, Pellegrino C, Varlet P, Labussiere M, Cresto N, Dieme MJ, Baulac M, Duyckaerts C, Kourdougli N, Chazal G, Devaux B, Rivera C, Miles R, Capelle L, Huberfeld G. Cortical GABAergic excitation contributes to epileptic activities around human glioma. Sci Transl Med. 2014; 6(244): 244ra89.

24. Kahle KT, Khanna AR, Duan J, Staley KJ, Delpire E, Poduri A. The KCC2 Cotransporter and Human Epilepsy. Neuroscientist. 2016; 22(6): 555–62.

25. Barmashenko G, Hefft S, Aertsen A, Kirschstein T, Köhling R. Positive shifts of the GABAA receptor reversal potential due to altered chloride homeostasis is widespread after status epilepticus. Epilepsia. 2011; 52(9): 1570–8.

26. Huberfeld G, Wittner L, Clemenceau S, Baulac M, Kaila K, Miles R, Rivera C. Perturbed Chloride Homeostasis and GABAergic Signaling in Human Temporal Lobe Epilepsy. J Neurosci. 2007; 27(37): 9866–73.

27. Pathak HR, Weissinger F, Terunuma M, Carlson GC, Hsu F-C, Moss SJ, Coulter DA. Disrupted dentate granule cell chloride regulation enhances synaptic excitability during development of temporal lobe epilepsy. J Neurosci. 2007; 27(51): 14012–22.

28. MacKenzie G, O'Toole KK, Moss SJ, Maguire J. Compromised GABAergic inhibition contributes to tumor-associated epilepsy. Epilepsy Research. 2016; 126: 185–96.

29. Aronica E, Boer K, Redeker S, Spliet WGM, van Rijen PC, Troost D, Gorter JA. Differential expression patterns of chloride transporters, Na+-K+-2Cl−-cotransporter and K+-Cl−-cotransporter, in epilepsy-associated malformations of cortical development. IBRO; 2007; 145(1): 185–96.

30. Campbell SL, Robel S, Cuddapah VA, Robert S, Buckingham SC, Kahle KT, Sontheimer H. GABAergic disinhibition and impaired KCC2 cotransporter activity underlie tumor-associated epilepsy. Glia. 2014; 63(1): 23–36.

31. Conti L, Palma E, Roseti C, Lauro C, Cipriani R, de Groot M, Aronica E, Limatola C. Anomalous levels of Cl− transporters cause a decrease of GABAergic inhibition in human peritumoral epileptic cortex. Epilepsia. 2011; 52(9): 1635–44.

32. Lee HHC, Walker JA, Williams JR, Goodier RJ, Payne JA, Moss SJ. Direct protein kinase C-dependent phosphorylation regulates the cell surface stability and activity of the potassium chloride cotransporter KCC2. J Biol Chem. 2007; 282(41): 29777–84.

33. Aronica E, Boer K, Becker A, Redeker S, Spliet WGM, van Rijen PC, Wittink F, Breit T, Wadman WJ, Lopes da Silva FH, Troost D, Gorter JA. Gene expression profile analysis of epilepsy-associated gangliogliomas. Neuroscience. 2008; 151(1): 272–92.

34. Eftekhari S, Mehvari Habibabadi J, Najafi Ziarani M, Hashemi Fesharaki SS, Gharakhani M, Mostafavi H, Joghataei MT, Beladimoghadam N, Rahimian E, Hadjighassem MR. Bumetanide reduces seizure frequency in patients with temporal lobe epilepsy. Epilepsia. 2012; 54(1): e9–e12.

35. Huberfeld G, Vecht CJ. Seizures and gliomas — towards a single therapeutic approach. Nat Rev Neurol. 2016; 12(4): 204–16.

36. Isoardo G, Morra I, Chiarle G, Audrito V, Deaglio S, Melcarne A, Junemann C, Naddeo M, Cogoni M, Valentini MC, Limberti A, Faccani F, Malavasi F, Faccani G. Different aquaporin-4 expression in glioblastoma multiforme patients with and without seizures. Mol Med. 2012; 18: 1147–51.

37. Haj-Yasein NN, Jensen V, Vindedal GF, Gundersen GA, Klungland A, Ottersen OP, Hvalby Ø, Nagelhus EA. Evidence that compromised K+ spatial buffering contributes to the epileptogenic effect of mutations in the human kir4.1 gene (KCNJ10). Glia. 2011; 59(11): 1635–42.

38. Marchi N, Angelov L, Masaryk T, Fazio V, Granata T, Hernandez N, Hallene K, Diglaw T, Franic L, Najm I, Janigro D. Seizure-promoting effect of blood-brain barrier disruption. Epilepsia. 2007; 48(4): 732–42.

39. van Vliet EA, da Costa Araujo S, Redeker S, van Schaik R, Aronica E, Gorter JA. Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. Brain. 2007; 130(2): 521–34.

40. Fieschi C, Lenzi GL, Zanette E, Orzi F, Passero S. Effects on EEG of the osmotic opening of the blood-brain barrier in rats. Life Sciences. 1980; 27(3): 239–43.

41. Seiffert E, Dreier JP, Ivens S, Bechmann I, Tomkins O, Heinemann U, Friedman A. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. J Neurosci. 2004; 24(36): 7829–36.

42. Mignot C, Boespflug-Tanguy O, Gelot A, Dautigny A, Pham-Dinh D, Rodriguez D. Alexander disease: putative mechanisms of an astrocytic encephalopathy. Cellular and Molecular Life Sciences (CMLS). 2004; 61(3): 369–85.

43. Pekny M, Stanness KA, Eliasson C, Betsholtz C, Janigro D. Impaired induction of blood-brain barrier properties in aortic endothelial cells by astrocytes from GFAP-deficient mice. Glia. 1998; 22(4): 390–400.

44. Heinemann U, Kaufer D, Friedman A. Blood-brain barrier dysfunction, TGF signaling,

and astrocyte dysfunction in epilepsy. Glia. 2012; 60(8): 1251–7.

45. Beaumont A, Whittle IR. The pathogenesis of tumour associated epilepsy. Acta Neurochir. 2000; 142(1): 1–15.

46. Savaskan NE, Heckel A, Hahnen E, Engelhorn T, Doerfler A, Ganslandt O, Nimsky C, Buchfelder M, Eyüpoglu IY. Small interfering RNA–mediated xCT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. Nat Med. 2008; 14(6): 629–32.

47. Naus CC, Bechberger JF, Paul DL. Gap junction gene expression in human seizure disorder. Exp Neurol. 1991; 111(2): 198–203.

48. Fonseca CG, Green CR, Nicholson LFB. Upregulation in astrocytic connexin 43 gap junction levels may exacerbate generalized seizures in mesial temporal lobe epilepsy. Brain Res. 2002; 929(1): 105–16.

49. Aronica E, Gorter JA, Jansen GH, Leenstra S, Yankaya B, Troost D. Expression of connexin 43 and connexin 32 gap-junction proteins in epilepsy-associated brain tumors and in the perilesional epileptic cortex. Acta Neuropathol. 2001; 101(5): 449–59.

50. Soroceanu L, Manning TJ, Sontheimer H. Reduced expression of connexin-43 and functional gap junction coupling in human gliomas. Glia. 2001; 33(2): 107–17.

51. You G, Sha Z, Jiang T. The pathogenesis of tumor-related epilepsy and its implications for clinical treatment. Seizure: European Journal of Epilepsy. 2012; 21(3): 153–9.

52. Steinhäuser C, Seifert G, Bedner P. Astrocyte dysfunction in temporal lobe epilepsy: K+ channels and gap junction coupling. Glia. 2012; 60(8): 1192–202.

53. Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, Postma TJ, Heimans JJ, van Dijk BW, de Munck JC, de Jongh A, Cover KS, Stam CJ. Disturbed functional connectivity in brain tumour patients: Evaluation by graph analysis of synchronization matrices. Clinical Neurophysiology. 2006; 117(9): 2039–49.

54. Bosma I, Reijneveld JC, Klein M, Douw L, van Dijk BW, Heimans JJ, Stam CJ. Disturbed functional brain networks and neurocognitive function in low-grade glioma patients: a graph theoretical analysis of resting-state MEG. Nonlinear Biomed Phys. 2009; 3(1): 9–11.

55. Derks J, Dirkson AR, de Witt Hamer PC, van Geest Q, Hulst HE, Barkhof F, Pouwels PJW, Geurts JJG, Reijneveld JC, Douw L. Connectomic profile and clinical phenotype in newly diagnosed glioma patients. NeuroImage: Clinical. 2017; 14(C): 87–96.

56. Esposito R, Mattei PA, Briganti C, Romani GL, Tartaro A, Caulo M. Modifications of Default-Mode Network Connectivity in Patients with Cerebral Glioma. PLoS ONE. 2012; 7(7): e40231–9.

57. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2010; 7(1): 31–40.

58. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. Neuropharmacology. 2013; 69: 16–24.

59. Rossi D, Volterra A. Astrocytic dysfunction: Insights on the role in neurodegeneration. Brain Research Bulletin. 2009; 80(4-5): 224–32.

60. Tarassishin L, Casper D, Lee SC. Aberrant Expression of Interleukin-1 and Inflammasome Activation in Human Malignant Gliomas. PLoS ONE. 2014; 9(7): e103432–14.

61. Thom M, Blümcke I, Aronica E. Long-Term Epilepsy-Associated Tumors. Brain Pathology. 2012; 22(3): 350–79.

62. Blümcke I, Aronica E, Becker A, Capper D, Coras R, Honavar M, Jacques TS, Kobow K, Miyata H, Mühlebner A, Pimentel J, Söylemezoğlu F, Thom M. Low-grade epilepsy-associated neuroepithelial tumours — the 2016 WHO classification. Nat Rev Neurol. 2016; 12(12): 732–40.

63. Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, Schmieder K, Wesseling P, Mawrin C, Hasselblatt M, Louis DN, Korshunov A, Pfister S, Hartmann C, Paulus W, Reifenberger G, Deimling A. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011; 121(3): 397–405.

64. Koelsche C, Wöhrer A, Jeibmann A, Schittenhelm J, Schindler G, Preusser M, Lasitschka F, Deimling von A, Capper D. Mutant BRAF V600E protein in ganglioglioma is predominantly expressed by neuronal tumor cells. Acta Neuropathol. 2013; 125(6): 891–900.

65. Qaddoumi I, Orisme W, Wen J, Santiago T, Gupta K, Dalton JD, Tang B, Haupfear K, Punchihewa C, Easton J, Mulder H, Boggs K, Shao Y, Rusch M, Becksfort J, Gupta P, Wang S, Lee RP, Brat D, Peter Collins V, Dahiya S, George D, Konomos W, Kurian KM, McFadden K, Serafini LN, Nickols H, Perry A, Shurtleff S, Gajjar A, Boop FA, Klimo PD, Mardis ER, Wilson RK, Baker SJ, Zhang J, Wu G, Downing JR, Tatevossian RG, Ellison DW. Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. Acta Neuropathol. 2016; 131(6): 833–45.

66. Prabowo AS, Iyer AM, Veersema TJ, Anink JJ, Schouten-van Meeteren AYN, Spliet WGM, van Rijen PC, Ferrier CH, Capper D, Thom M, Aronica E. BRAF V600E Mutation Is Associated with mTOR Signaling Activation in Glioneuronal Tumors. Brain Pathology. 2013; 24(1): 52–66.

67. Dahiya S, Haydon DH, Alvarado D, Gurnett CA, Gutmann DH, Leonard JR. BRAF V600E mutation is a negative prognosticator in pediatric ganglioglioma. Acta

Neuropathol. 2013; 125(6): 901–10.

68. Dougherty MJ, Santi M, Brose MS, Ma C, Resnick AC, Sievert AJ, Storm PB, Biegel JA. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. Neuro-Oncology. 2010; 12(7): 621–30.

69. Chappé C, Padovani L, Scavarda D, Forest F, Nanni-Metellus I, Loundou A, Mercurio S, Fina F, Lena G, Colin C, Figarella-Branger D. Dysembryoplastic Neuroepithelial Tumors Share with Pleomorphic Xanthoastrocytomas and Gangliogliomas BRAF V600E Mutation and Expression. Brain Pathology. 2013; 23(5): 574–83.

70. Lee D, Cho YH, Kang SY, Yoon N, Sung CO, Suh Y-L. BRAF V600E mutations are frequent in dysembryoplastic neuroepithelial tumors and subependymal giant cell astrocytomas. J Surg Oncol. 2015; 111(3): 359–64.

71. Rivera B, Gayden T, Carrot-Zhang J, Nadaf J, Boshari T, Faury D, Zeinieh M, Blanc R, Burk DL, Fahiminiya S, Bareke E, Schüller U, Monoranu CM, Sträter R, Kerl K, Niederstadt T, Kurlemann G, Ellezam B, Michalak Z, Thom M, Lockhart PJ, Leventer RJ, Ohm M, MacGregor D, Jones D, Karamchandani J, Greenwood CMT, Berghuis AM, Bens S, Siebert R, Zakrzewska M, Liberski PP, Zakrzewski K, Sisodiya SM, Paulus W, Albrecht S, Hasselblatt M, Jabado N, Foulkes WD, Majewski J. Germline and somatic FGFR1 abnormalities in dysembryoplastic neuroepithelial tumors. Acta Neuropathol. 2016; 131(6): 847-63.

72. Stone TJ, Keeley A, Virasami A, Harkness W, Tisdall M, Izquierdo Delgado E, Gutteridge A, Brooks T, Kristiansen M, Chalker J, Wilkhu L, Mifsud W, Apps J, Thom M, Hubank M, Forshew T, Cross JH, Hargrave D, Ham J, Jacques TS. Comprehensive molecular characterisation of epilepsy-associated glioneuronal tumours. Acta Neuropathol. 2017; Epub ahead of print.

73. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007; 114(2): 97–109.

74. Preusser M, Hoischen A, Novak K, Czech T, Prayer D, Hainfellner JA, Baumgartner C, Woermann FG, Tuxhorn IE, Pannek HW, Bergmann M, Radlwimmer B, Villagrán R, Weber RG, Hans VH. Angiocentric glioma: report of clinico-pathologic and genetic findings in 8 cases. Am J Surg Pathol. 2007; 31(11): 1709–18.

75. Bandopadhayay P, Ramkissoon LA, Jain P, Bergthold G, Wala J, Zeid R, Schumacher SE, Urbanski L, O'Rourke R, Gibson WJ, Pelton K, Ramkissoon SH, Han HJ, Zhu Y, Choudhari N, Silva A, Boucher K, Henn RE, Kang YJ, Knoff D, Paolella BR, Gladden-Young A, Varlet P, Pages M, Horowitz PM, Federation A, Malkin H, Tracy AA, Seepo S, Ducar M, Van Hummelen P, Santi M, Buccoliero AM, Scagnet M, Bowers DC, Giannini C, Puget S, Hawkins C, Tabori U, Klekner A, Bognar L, Burger PC, Eberhart C, Rodriguez FJ, Hill DA, Mueller S, Haas-Kogan DA, Phillips JJ, Santagata S, Stiles CD, Bradner JE, Jabado N, Goren A, Grill J, Ligon AH, Goumnerova L, Waanders AJ, Storm PB, Kieran MW, Ligon KL, Beroukhim R, Resnick AC. MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity

through a tripartite mechanism. Nat Genet. 2016; 48(3): 273–82.

76. Huse JT, Edgar M, Halliday J, Mikolaenko I, Lavi E, Rosenblum MK. Multinodular and Vacuolating Neuronal Tumors of the Cerebrum: 10 Cases of a Distinctive Seizure-Associated Lesion. Brain Pathology. 2013; 23(5): 515–24.

77. Thom M, Liu J, Bongaarts A, Reinten RJ, Paradiso B, Jäger HR, Reeves C, Somani A, An S, Marsdon D, McEvoy A, Miserocchi A, Thorne L, Newman F, Bucur S, Honavar M, Jacques T, Aronica E. Multinodular and vacuolating neuronal tumors in epilepsy: dysplasia or neoplasia? Brain Pathology. 2017; 145: 185–17.

78. Cathcart SJ, Klug JR, Helvey JT, L White M, Gard AP, McComb RD. Multinodular and Vacuolating Neuronal Tumor: A Rare Seizure-associated Entity. Am J Surg Pathol. 2017; 41(7): 1005–10.

79. Yamaguchi M, Komori T, Nakata Y, Yagishita A, Morino M, Isozaki E. Multinodular and vacuolating neuronal tumor affecting amygdala and hippocampus: A quasi-tumor? Pathol Int. 2015; 66(1): 34–41.

80. Fukushima S, Yoshida A, Narita Y, Arita H, Ohno M, Miyakita Y, Ichimura K, Shibui S. Multinodular and vacuolating neuronal tumor of the cerebrum. Brain Tumor Pathol. 2014; 32(2): 131–6.

81. Bodi I, Curran O, Selway R, Elwes R, Burrone J, Laxton R, Al-Sarraj S, Honavar M. Two cases of multinodular and vacuolating neuronal tumour. Acta Neuropathol Commun. 2014; 2: 7.

82. Nagaishi M, Yokoo H, Nobusawa S, Fujii Y, Sugiura Y, Suzuki R, Tanaka Y, Suzuki K, Hyodo A. Localized overexpression of alpha-internexin within nodules in multinodular and vacuolating neuronal tumors. Neuropathology. 2015; 35(6): 561–8.

83. Gonzalez-Quarante LH, Ruiz-Juretschke F, Sola Vendrell E, Gil de Sagredo del Corral OL, Agarwal V, Garcia-Leal R. Multinodular and vacuolating neuronal tumor of the cerebrum. A rare entity. New case and review of the literature. Neurocirugía. 2017; Epub ahead of print.

84. Huse JT, Snuderl M, Jones DTW, Brathwaite CD, Altman N, Lavi E, Saffery R, Sexton-Oates A, Blümcke I, Capper D, Karajannis MA, Benayed R, Chavez L, Thomas C, Serrano J, Borsu L, Ladanyi M, Rosenblum MK. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): an epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. Acta Neuropathol. 2016; 133(3): 417–29.

85. Blümcke I, Luyken C, Urbach H, Schramm J, Wiestler OD. An isomorphic subtype of long-term epilepsy-associated astrocytomas associated with benign prognosis. Acta Neuropathol. 2004; 107(5): 381–8.

86. Schramm J, Luyken C, Urbach H, Fimmers R, Blümcke I. Evidence for a Clinically

Distinct New Subtype of Grade II Astrocytomas in Patients with Long-term Epilepsy. Neurosurgery. 2004; 55(2): 340–8.

87. Jones DTW, Kocialkowski S, Liu L, Pearson DM, Backlund LM, Ichimura K, Collins VP. Tandem Duplication Producing a Novel Oncogenic BRAF Fusion Gene Defines the Majority of Pilocytic Astrocytomas. Cancer Res. 2008; 68(21): 8673–7.

88. Pfister S, Janzarik WG, Remke M, Ernst A, Werft W, Becker N, Toedt G, Wittmann A, Kratz C, Olbrich H, Ahmadi R, Thieme B, Joos S, Radlwimmer B, Kulozik A, Pietsch T, Herold-Mende C, Gnekow A, Reifenberger G, Korshunov A, Scheurlen W, Omran H, Lichter P. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest. 2008; 118(5): 1739–49.

89. Jones DTW, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz H-J, Zichner T, Lambert SR, Ryzhova M, Quang DAK, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Şeker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, Kalle von C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho Y-J, Pomeroy SL, Deimling von A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo M-L, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, International Cancer Genome Consortium PedBrain Tumor Project. Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet. 2013; 45(8): 927–32.

90. Zhang J, Wu G, Miller CP, Tatevossian RG, Dalton JD, Tang B, Orisme W, Punchihewa C, Parker M, Qaddoumi I, Boop FA, Lu C, Kandoth C, Ding L, Lee R, Huether R, Chen X, Hedlund E, Nagahawatte P, Rusch M, Boggs K, Cheng J, Becksfort J, Ma J, Song G, Li Y, Wei L, Wang J, Shurtleff S, Easton J, Zhao D, Fulton RS, Fulton LL, Dooling DJ, Vadodaria B, Mulder HL, Tang C, Ochoa K, Mullighan CG, Gajjar A, Kriwacki R, Sheer D, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Baker SJ, Ellison DW, St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet. 2013; 45(6): 602–12.

91. Bettegowda C, Agrawal N, Jiao Y, Wang Y, Wood LD, Rodriguez FJ, Hruban RH, Gallia GL, Binder ZA, Riggins CJ, Salmasi V, Riggins GJ, Reitman ZJ, Rasheed A, Keir S, Shinjo S, Marie S, McLendon R, Jallo G, Vogelstein B, Bigner D, Yan H, Kinzler KW, Papadopoulos N. Exomic sequencing of four rare central nervous system tumor types. Oncotarget. 2013; 4(4): 572–83.

92. Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, Batchelor TT, Ligon KL, Iafrate AJ, Ligon AH, Louis DN, Santagata S. BRAF V600E Mutations Are Common in Pleomorphic Xanthoastrocytoma: Diagnostic and Therapeutic Implications. PLoS ONE. 2011; 6(3): e17948–9.

93. Koelsche C, Sahm F, Wöhrer A, Jeibmann A, Schittenhelm J, Kohlhof P, Preusser M, Romeike B, Dohmen-Scheufler H, Hartmann C, Mittelbronn M, Becker A, Deimling von A, Capper D. BRAF-Mutated Pleomorphic Xanthoastrocytoma is Associated with Temporal Location, Reticulin Fiber Deposition and CD34 Expression. Brain Pathology. 2014; 24(3): 221–9.

94. Weber RG, Hoischen A, Ehrler M, Zipper P, Kaulich K, Blaschke B, Becker AJ, Weber-Mangal S, Jauch A, Radlwimmer B, Schramm J, Wiestler OD, Lichter P, Reifenberger G. Frequent loss of chromosome 9, homozygous CDKN2A/p14ARF/CDKN2B deletion and low TSC1 mRNA expression in pleomorphic xanthoastrocytomas. Oncogene. 2006; 26(7): 1088–97.

95. Vecht C, Duran-Peña A, Houillier C, Durand T, Capelle L, Huberfeld G. Seizure response to perampanel in drug-resistant epilepsy with gliomas: early observations. J Neurooncol. 2017; 133(3): 603–7.

96. Shih KC, Shastry M, Williams JT, Jelsma PF, Abram SR, Ayyanar K, Burris HA, Infante JR. Successful treatment with dabrafenib (GSK2118436) in a patient with ganglioglioma. Journal of Clinical Oncology. 2014; 32(29): e98–e100.

| **Ganglioglioma** | |
|---|---|
| **Cohort** | **BRAF-V600E+** |
| Schindler *et al.* [63] | 17/83 (20%) |
| Koelsche *et al.* [64] | 41/71 (58%) |
| Qaddoumi *et al.* [65] | 6/17 (35%) |
| Prabowo *et al.* [66] | 38/93 (41%) |
| Dahiya *et al.* [67] | 18/47 (38%) |
| Dougherty *et al.* [68] | 9/18 (50%) |
| **DNET** | |
| Chappé *et al.* [69] | 6/20 (30%) |
| Lee *et al.* [70] | 26/51 (51%) |
| Prabowo *et al.* [66] | 17/55 (31%) |
| Dougherty *et al.* [68] | 0/3 (0%) |
| Rivera *et al.* [71] | 0/43 (0%) |

| **Tumour** | **Common Pathogenic Mutations** | **Other Pathogenic Mutations** |
|---|---|---|
| **Glioneuronal Group 1** | *BRAF*-V600E | N/A |
| **Glioneuronal Group 2** | *FGFR1* | N/A |
| **Pilocytic Astrocytoma** | *KIAA1549-BRAF* fusion | *BRAF*-V600E |
| **PXA** | *BRAF*-V600E | *CDKN2A, CDKN2B* |
| **Isomorphic Astrocytoma** | N/A | N/A |
| **Angiocentric Glioma** | *MYB-QKI* fusion | *MYB-ESR1* fusion, *QKI* rearrangement |
| **MVNT** | N/A | N/A |
| **PLNTY** | N/A | *BRAF*-V600E, *FGFR2* fusion, *FGFR3* fusion |