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REVIEW ARTICLE

Tumor-associated epilepsy and glioma: Are there common genetic pathways?

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Abstract
Background. Patients with glioma exhibit a great variability in clinical symptoms apart from variations in response to therapy and survival. Many patients present with epileptic seizures at disease onset, especially in case of low-grade gliomas, but not all have seizures. A large proportion of patients develop refractory seizures. It is likely that the variability in epileptic symptoms cannot exclusively be explained by tumor-related factors, but rather reflects complex interaction between tumor-related, environmental and hereditary factors. *Material and methods.* No data exist on susceptibility genes associated with epileptic symptoms in patients with glioma. However, an increasing number of candidate genes have been proposed for other focal epilepsies such as temporal lobe epilepsy. Some of the susceptibility candidate genes associated with focal epilepsy may contribute to epileptic symptoms also in patients with glioma. *Results.* This review presents an update on studies on genetic polymorphisms and focal epilepsy and brings forward putative candidate genes for tumor-associated epilepsy, based on the assumption that common etiological pathways may exist for glioma development and glioma-associated seizures. *Conclusion.* Genes involved in the immune response, in synaptic transmission and in cell cycle control are discussed that may play a role in the pathogenesis of tumor growth as well as epileptic symptoms in patients with gliomas.

Gliomas

Gliomas of astrocytic, oligodendrocytic and ependymal origin comprise about 40% of all adult primary brain tumors [1,2]. The most frequent and most malignant histological subtype is the glioblastoma, with an annual incidence of 4–5 per 100 000 and a median age at diagnosis of around 60 years [3]. The annual incidence of low-grade gliomas is estimated to 1–2 per 100 000 inhabitants [3]. Despite multimodal treatment approaches consisting of surgery, radiotherapy and chemotherapy, the prognosis of patients with glioblastoma is still poor [4]. The median survival of adults with low-grade gliomas is around 5–10 years, but for most if not all patients the disease has a fatal outcome. Gliomas account for as many as 26 000 USA and European deaths each year.

Apart from high-dose ionizing radiation as an established risk factor and a consistent inverse relationship of glioma with allergies and asthma, the etiology of gliomas is largely unknown [2]. Only 5% of all glioma cases constitute familiar forms, leaving the vast majority of patients with sporadic gliomas. Evidence strongly suggests that inherited susceptibility plays a role with two-fold increased risk of glioma among first-degree relatives of glioma cases [5]. Apart from rare Mendelian cancer predisposition syndromes, the genetic basis of glioma susceptibility has not been fully elucidated.

Genetic susceptibility and glioma

A recent report on the genetic basis of susceptibility to gliomas showed several candidate genes associated with increased overall risk of glioma, although

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presently few associations have been confirmed in several independent data sets [6]. The most commonly studied candidate genes for glioma risk are genes involved in cell cycle control, DNA repair and immune response. Table I shows examples of genes and their specific polymorphisms that have shown to be associated with an altered risk for glioma development [7–17]. CHAF1A and P53 have been associated in single studies for glioma and glioblastoma respectively [18]. In addition, a recent pooled analysis of four US data sets showed associations with DNA repair genes and glioblastoma in 1 000 glioblastoma cases and 2 000 controls [19]. Several studies have associated infection and immune function with a decreased risk of glioma [7]. Allergies have shown to be inversely correlated to gliomas and consistent associations were reported for an IL13 polymorphism and an IL4R haplotype, although it remains unclear whether allergies protect against tumors or whether immunosuppressive gliomas inhibit allergies [20,21].

Epilepsy and gliomas

Focal epileptic seizures are among the most common symptoms at disease onset in patients with gliomas. Seizures can frequently predate other symptoms or diagnosis by many years [22]. There is an inverse relationship between tumor growth rate and seizure risk, and symptomatic seizures are significantly more common in low-grade than high-grade gliomas [23]. Up to 80–90% of all patients with low-grade gliomas experience seizures or epilepsy, but not all have seizures in spite of similar tumor localization and histology (Figure 1). Epilepsy may be the only symptom for months or years in the non-progressive phase of the disease. In a recent study, approximately half of the patients with low-grade gliomas who presented with seizures were pharmacoresistant before surgery [24].

Other important factors underlying the development of epilepsy in patients with glioma besides the growth rate of the tumor are the localization in the brain and the proximity with the cortical gray matter

Table I. Some examples of case-control studies of gene polymorphisms showing associations with altered glioma risk.

| First Author	Gene and specific polymorphism	Tumor type	Number of cases and controls
Brenner [7]	Cytokines IL-4 (rs224348) IL-6 (rs1800795)	Glioma	756 cases, 1190 controls
Rajaraman [8]	Cell cycle CCND1 (rs603965) CCNH (rs2266690) MDM2 (rs769412)	Glioma	388 cases, 533 controls
Liu [9]	DNA repair ERCC1 (3'UTR) XRCC1 (R399Q) APEX1 (E148D) PARP1 (A762V) MGMT (F84L) LIG1 (5'UTR)	Glioma	373 cases, 365 controls
Carpentier [10]	Telomerase hTERT (MNS16A)	Glioblastoma (GB) & Anaplastic astrocytoma (AA)	205 GB, 147 AA, 305 controls
Costa [11]	EGF (EGF+61)	Glioma	197 cases, 570 controls
Lu [12]	Promoter Matrix metalloproteinase MMP-1-1607 1G/1G MMP-1 1G-MMP-3 6A	Astrocytoma	236 cases, 366 controls
Parhar [13]	P53 codon 72 P53 Arg72Pro	Glioma (including pediatric cases)	92 adult cases, 43 pediatric cases, 71 controls
Bhowmick [14]	EGF-receptor (EGFR 5'UTR, G/A & G/G genotype)	Glioblastoma (GB)	31 primary GB, 11 secondary GB 78 controls
Wrensch [15]	Glutathione-S-transferase GSTP I105V	GB, astrocytoma (A), oligodendro-glioma (OD), oli-goastrocytoma (OA)	179 GB, 62A, 94 OD or OA, 32 others, 428 controls
Wang [16]	DNA repair XRCC/ G6721T (G/T & T/T genotype)	Glioma	309 cases, 342 controls
Frigerio [17]	Tumour necrosis factor TNFb4	Glioblastoma	58 patients, 95 controls
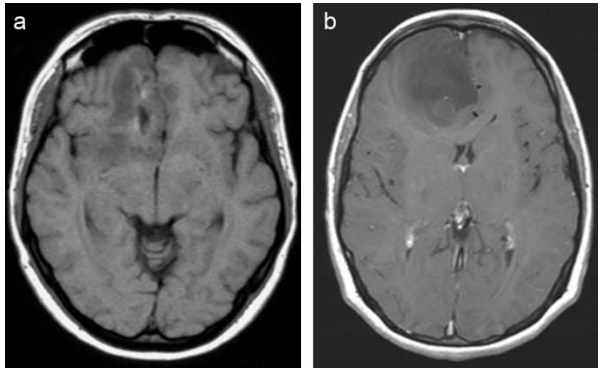
Figure 1. MRI (T1-weighted images) of two patients with an oligodendroglioma (grade II) in the right frontal lobe, both presenting with focal epileptic seizures as the first symptoms.
a) This patient became seizure-free on antiepileptic drugs after an initial seizure.
b) This patient developed pharmacoresistent seizures in spite of multiple antiepileptic drugs.

[23]. Tumors localized in the vicinity of the primary motor cortex and tumors with limbic and perilimbic cortical localization are highly epileptogenic, whereas occipital tumors are less likely to manifest with seizures. Epileptic seizures in high-grade gliomas are less frequent but may be more difficult to control. The pathogenesis of seizure development is likely to occur by different mechanisms for high- and low-grade gliomas [22,25]. In fast growing high-grade gliomas the focal peri-tumoral ischaemia and deafferentiation of cortical areas due to mass effect may be causative factors, whereas gliosis and chronic inflammatory changes in peri-tumoral regions of slowly growing gliomas may predispose for epileptic seizures (Figure 2). Increased levels of Fe^{3+} ions in intra- or peri-tumoral areas, due to small bleedings from pathological blood vessels, may also contribute to the development of tumor-associated seizures and are more likely to occur in high-grade gliomas [22]. Our knowledge of tumor-associated epileptogenicity, however, is limited and current therapy is far from perfect [26].

Epileptic seizures and survival in patients with glioma

A deeper understanding of the correlation between symptoms and course of disease for patients with gliomas is of importance in clinical neuro-oncology. The recurrence of epileptic seizures after a long seizure-free period, for example, may be the first sign of progressive disease before radiological progression is visible, but this is not always the case. Little is known on the impact of seizures on survival for patients with high-grade glioma, but for low-grade gliomas a number of studies have established an association between a more favourable prognosis and epileptic seizures at disease onset [27]. As stated previously, epileptic seizures as initial symptoms in low-grade gliomas are also strongly correlated to a more cortical tumor localization, in contrast to patient with centrally localized tumors who do not frequently present with seizures and have a poor prognosis [27]. We have recently found that patients with low-grade glioma who presented with seizures as initial symptoms but became seizure-free during the early stage of disease had a longer survival than those with recurrent seizures [28]. These findings suggest that the specific symptoms of disease may reflect not only the localization of the tumor in the brain but also the biological behavior of the tumor, and warrant further studies of putative common pathogenetic pathways for course and symptoms of disease.

Genetic variability and focal epilepsy

The genetic background for tumor-associated epilepsy is unknown and no data are available on the genetic variability associated with the presence of epileptic seizures and the outcome in terms of response to antiepileptic drugs in patients with gliomas. More is known though on the genetics of other non tumor-associated focal epilepsies. A few
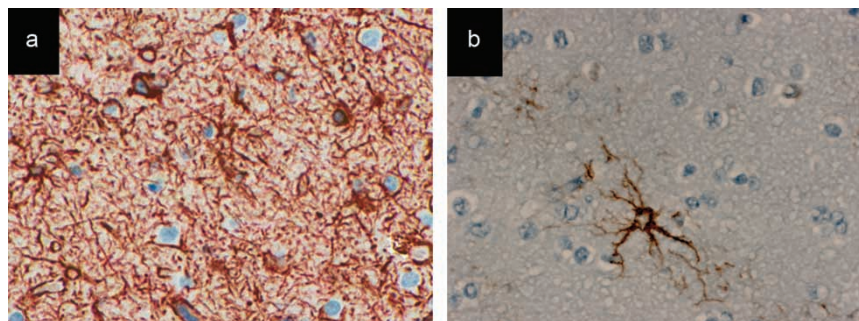

Figure 2. Immunohistochemical stainings with antibodies for the astrocytic marker GFAP (glial fibrillary acidic protein) of the peri-tumoural cortices of two different samples of diffuse astrocytomas (WHO grade II).
a) A significant increase of reactive astrocytes is demonstrated in the peri-tumoural cortex of this patient with chronic epileptic seizures, compared to. b) the peri-tumoural cortex of a patient who did not have any epileptic seizures.

inherited syndromes for focal epilepsies have been described [29–31], and an increasing number of candidate genes have been proposed for focal epilepsies during recent years [32]. Since the focus of this review is on genetic association studies, we performed a literature search on susceptibility genes for all types of focal epilepsies. We searched for studies published in PubMed in the English language during the last ten years, with a final search performed in September 2008. Tables II–IV present a systematic overview of these studies, demonstrating positive as well as negative associations for the different candidate genes [33–48].

A number of single studies have reported positive associations between polymorphisms and adult focal epilepsies that have not yet been confirmed by others and therefore have not been included in the tables. One such example is functional polymorphisms of the prodynorphin gene promoter (PDYN) that were found in familial cases of idiopathic generalized epilepsy. Endogenous dynorphin is an opioid with several physiological effects including a role in the regulation of hippocampal excitability, indicating a probable anticonvulsant effect [49]. Patients with temporal lobe epilepsy carrying the low frequency PDYN allele showed a higher risk of developing secondary generalized seizures and status epilepticus [50]. PDYN may therefore be a general risk factor for epilepsy, but further studies are needed to confirm this hypothesis. In another single study, an allele variant of the cellular prion protein gene was identified at codon 171 (Asn171Ser) in a Brazilian cohort of patients with refractory temporal lobe epilepsy [51].

Putative common pathways for glioma and tumor-associated epilepsy

Based on the assumptions that 1) some of the susceptibility genes associated with focal epilepsy may be involved in tumor-associated seizures, and 2) the biological activity of the tumor may to some extent be related to the epileptic symptoms of the patient, we discuss here some putative common pathways for glioma development and tumor-associated epilepsy.

Immune response

Several studies have associated infection and immune function with a decreased risk of glioma [7,20,21]. Immunological factors are likely to play a role also in tumor-associated epilepsy, and proinflammatory cytokines and their receptors have been suggested to be involved in the pathogenesis of epilepsy. Cytokines have modulating effects on neurotoxic neurotransmitters that are discharged during excitation or inflammation in the central nervous system. For many patients with gliomas the epileptic focus is not contiguous with the tumor, and seizure etiology involves peri-tumoral brain regions in which immune mediated neurochemical changes by microglial components are known to occur [22,52,53]. An immune-mediated neuronal damage of the peri-tumoral brain area, coupled to

Table II. Case-control studies on polymorphisms of interleukins (IL) and focal epilepsy.

First Author	Specific polymorphism	Epilepsy type	Nr of patients and controls	Outcome statistics and p-value
Kanemoto [33]	IL- 1β- 511	TLE-HS+	50 cases and 112 controls	$\chi^2 = 9.55$ p < 0.017
Kanemoto [34]	IL- 1β- 511	TLE-HS+ and PFC	66 cases, 133 controls	TLE-HS+: $\chi^2 = 9.38$ p $= 0.0022$ PFC: $\chi^2 = 9.90$ P $= 0.0016$
Ozkara [35]	IL-1β-511; IL-1β+3953; IL-1α−889	TLE-HS+	47 cases, 99 controls	NS
Heils [36]	IL-1β-511	TLE-HS+	86 cases, 133 controls	$\chi^2 = 0.436$ p $= 0.804$
Buono [37]	IL-1β −511	TLE-HS+	61 cases, 119 controls	$\chi^2 = 5.22$ p $= 0.09$
Jin [38]	IL-1β- 511	TLE-HS+ and TLE-HS-	112 cases, 115 controls	NS

TLE: temporal lobe epilepsy.
TLE-HS+: temporal lobe epilepsy with hippocampal sclerosis.
TLE-HS-: temporal lobe epilepsy without hippocampal sclerosis.
PFC: prolonged febrile convulsions.

Table III. Case-control studies on polymorphisms of GABA receptors and serotonin transporters and focal epilepsy.

First Author	Gene, specific poly-morphisms	Epilepsy type	Number of patients and controls	P-value, odds ratio and confidence interval
Gambardella [39]	GABA (B) receptor G1465A	Non-lesional TLE	141 cases and 372 controls	OR =6.47; CI =2.02-20.75 p =0.003
Ma [40]	G1465A	TLE preceded by febrile seizures (FS)	120 cases, 218 controls	NS
Ma [41]	GABRA1, GABRA5, GABRG2, GABRD	Familial focal epilepsy preceded by FS	74 cases, 118 controls	NS
Manna [42]	Serotonin transporter (5-HTT) 5-HTTLPR 5-HTTVNTR	TLE	276 cases, 309 controls	5-HTTLPR: p =0.0086; 5-HTTVNTR: NS

the balance between stimulatory and inhibitory cytokines, may contribute to the development of tumor-related epilepsy [53].

Synaptic transmission by GABA

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the central nervous system. GABA acts mainly on two receptor types, type A and type B, which control neurotransmitter release and postsynaptic silencing of excitatory neurotransmission. Although the exact role of GABA in the development of epilepsy is not clear, there is evidence that dysfunction of both pre- and postsynaptic GABA-B receptor mediated processes contributes to temporal lobe epilepsy [54–56]. No association studies so far have coupled polymorphisms of GABAR subunits to an altered glioma risk, but several reports support a possible role of GABA in glioma development. Both astrocytes and microglia in the brain express the peripheral-type benzodiazepine receptor (PBR), which are multi-protein complexes located mainly at the outer mitochondrial membrane with GABAergic properties. PBR are widely expressed on different types of tumor cells [57]. The binding density of PBR is thought to correlate with the proliferative activity of the tumor, and high levels of PBR ligands were correlated with the tumorigenicity of glioma cells in vitro [58]. Consistently, PBR protein expression in astrocytoma samples strongly correlated with the histological malignancy grade of the tumor and with patient survival, with highest levels found in glioblastoma [59]. Interestingly, GABA may also play a direct immunomodulatory role in the brain, shown by the formation of functional extrasynaptic-like GABA channels on pathogenic T lymphocytes entering the brain [60]. Such immunomodulation by GABA may cause neurochemical changes in intra- and peri-tumoral regions, thereby affecting tumor growth as well as tumor-associated seizures.

Table IV. Studies on polymorphisms of apolipoprotein E (ApoE) and brain-derived neurotrophic factor (BDNF) and focal epilepsy.

First Author	Gene, specific polymorphism	Epilepsy type	Type of study	Number of patients and control group	Statistics and P-value
Blumcke [43]	Apo E	TLE with or without Ammons horn sclerosis (AHS)	Genetic linkage study	125 patients (65 TLE-AHS+, 53 TLE-AHS-)	NS
Gambardella [44]	Apo E −491 A/T	Non-lesional TLE	Case- control	63 patients, 220 controls	NS
Yeni [45]	Apo E4	Mesial TLE–HS	Case- control	47 cases, 62 controls	OR =1.06 CI =0.38-2.95 p >0.05
Briellmann [46]	ApoE4	Chronic TLE	No controls	43 patients, 31 HS +	ApoE4 may have impact on earlier onset of seizures p =0.004
Kanemoto [47]	ProBDNF 240T	Focal epilepsy	Case- control	219 cases, 311 controls	X^2 =8.59 p =0.0034
Lohoff [48]	BDNF C240T Val66Met	TLE	Case- control	151 cases, 189 controls	NS

Synaptic transmission by serotonin

Serotonin is released by presynaptic neurons and its action is terminated by re-uptake via the serotonin transporter protein. Variations in serotonergic activity are linked to both the development of epileptic foci and the severity of seizures [61]. A number of association studies have shown functional polymorphisms of the serotonin transporter promoter region in various psychiatric disorders, but so far only one study confirmed two previously identified polymorphisms of the serotonin transporter gene in patients with focal epilepsy [42]. The role of serotonin in gliomas is unclear, and no polymorphisms of serotonin-related genes have been associated with the disease. However, glioblastoma cells express the serotonin receptor 5-HT7, and stimulation of this receptor couples to multiple second messenger systems that amongst others can induce the expression of neurotrophic factors [62]. Upregulation of glial cell line-derived neurotrophic factor (GDNF) through serotonin receptors is one of the gene-gene interactions that has been demonstrated in patients with depression treated by antidepressants, but may occur in a wider variety of brain disorders including gliomas [63].

Synaptic transmission by glutamate

Although not confirmed by any association studies, a role for glutamate in both tumor-associated seizures and in glioma is widely accepted [64]. Glioma cells release glutamate, which causes excitotoxic death of surrounding neurons as one of the mechanisms for their destructive and invasive growth in the brain [65]. The release of glutamate occurs primarily via a Na+-independent cystine-glutamate exchanger, and may also contribute to seizures that start in the peri-tumoral regions. Animal studies in which human gliomas were xenographed into mice showed that chronic inhibition of glutamate release leads to smaller and less invasive tumors compared to controls [66]. Thus, future studies of genetic variability of genes involved in glutamate release, including GluR1, the most abundant AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptor subunit in gliomas, and the Na+-independent cystine-glutamate exchanger, are of great interest in patients with glioma-associated seizures.

Neurotrophic factors

Brain-derived neurotrophic factor (BDNF) regulates neuronal morphology and synaptogenesis and is known to exhibit neuroprotective effects in diverse areas of the central nervous system during development [67]. BDNF promotes neuronal survival and differentiation, and modulates synaptic transmission by increasing NMDA (N-methyl-D-aspartic) receptor activity [68]. Expression of BDNF was shown in the neuronal component of gangliogliomas and co-localized with NMDA receptors in these tumors [68]. Thus, BDNF and other neurotrophic factors in the brain may be involved in the growth regulation and epileptogenesis of tumors of glioneuronal origin.

Cell cycle control and DNA repair

Polymorphisms in a number of cell cycle control and DNA repair genes have been associated with glioma risk [19]. It is not known whether these genes may have a role also in the development of focal epilepsy. Interestingly, a recent gene expression profile analysis of epilepsy-associated gangliogliomas revealed altered expression levels of genes involved in the immune system and synaptic transmission, as well as in cell cycle control [69]. Increased expression levels of cyclin D1 and cyclin-dependent kinases (CDK) were found compared to normal control tissues, suggesting a role for these genes in the pathogenesis and possibly also the epileptogenesis of these lesions.

Apolipoprotein E

The apolipoprotein E (ApoE) ε4 allele is by far the most important genetic determinant of susceptibility to Alzheimer disease. ApoE promotes the deposition of β-amyloid (Aβ) in the brain parenchyma [70]. Mackenzie and Miller showed the occurrence of senile plaques in temporal lobe epilepsy [71], an observation which was later confirmed by the finding of increased levels of Aβ precursor protein in surgically resected human temporal lobe tissue [72]. In accordance, ApoE was shown a susceptibility gene for temporal lobe epilepsy by several studies, although negative findings have also been reported [43–46]. A role for apoE in glioma through delivery of lipids to tumor cells has been proposed [73]. Tau-associated neurodegenerative changes were found in gangliogliomas in an age-dependent quantity, but the distribution of ApoE genotypes was similar among those with tumors that contained tau-associated neuropathology and those that did not [74].

Conclusions

Studies of genetic variants as a causal factor to focal epilepsy have brought forward an increasing number of candidate genes. In this review, we describe several examples of association studies on this issue and hypothesize that some of the identified candidate

genes, such as genes involved in the immune response, cell cycle control and synaptic transmission, may be of importance also for tumor-associated epilepsy. We also bring forward some highly interesting candidates, such as genes involved in the glutamate system, for which no association studies have been reported yet.

Unfortunately many studies have used inadequate sample size with limited statistical power to detect the low odds ratios that low-penetrance alleles are likely to confer. In addition, we found many examples of follow-up studies that have not been able to confirm initial positive association studies. This could be due to several reasons such as lack of statistical power, non-associations, chance findings, differences in study design and studies of different populations.

Large multi centre studies including well characterized cases of low- and high-grade gliomas with and without symptomatic seizures are required to identify the underlying genetic variability and to increase our insight into the pathogenesis of tumor-related epilepsy and the possible overlapping pathways with glioma development. This is best studied by a first agnostic genome wide approach to identify candidate genes, subsequently needing independent confirmation in separate data sets. Such an approach may provide an important tool for the clinical management of patients with glioma suffering from epileptic seizures in the future.

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