Molecular Neuropathology of Epilepsy-Associated Glioneuronal Malformations

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Abstract

Glioneuronal malformations (malformations of cortical development [MCD]) include focal cortical dysplasias (FCD) as well as highly differentiated glioneuronal tumors (i.e., gangliogliomas) and constitute frequent findings in patients with pharmacoresistent focal epilepsies. Tailored resection strategies evolved as promising treatment options and allow a systematic neuropathologic and molecular biologic examination of the epileptogenic area in these patients. The histopathologic appearance and immunophenotype of glioneuronal lesions are, however, characterized by numerous similarities and suggest impaired proliferation, migration, and differentiation of neural precursor cells to play a pathogenetic role. Recent studies point toward molecular alterations within a variety of genes and pathways involved in development of the central nervous system, neuronal growth, and maturation. Compromised signaling within insulin- or reelin-transduction cascades are common findings and were associated with specific MCD entities. Unraveling pathogenic mechanisms may advance refined classification systems for epilepsy-associated malformations and open new avenues for the development of targeted treatment strategies in pharmacoresistent focal epilepsies associated with cortical malformations.

Key Words: Cortical malformations, Epilepsy, Ganglioglioma, Tuberous sclerosis.

INTRODUCTION

Epilepsies represent frequent neurologic disorders that affect approximately 1% of the population worldwide (1, 2). However, a considerable number of patients do not respond to currently available antiepileptic drugs (3). Clinical, imaging, and neuropathologic evidence for local seizure onset identify candidate patients who will benefit from tailored surgical resection strategies (4–7). In addition, anatomically and physiologically well-characterized human biopsy material offers unique research opportunities to address underlying pathophysiologic alterations in the disease tissue (8).

Focal seizure onset in the mesiobasal temporal lobe (temporal lobe epilepsy [TLE]) can be most frequently observed in patients who underwent epilepsy surgery. Subsequent histopathologic evaluation of surgical specimens is mandatory in determining the morphologic/cellular correlate of the epileptogenic area. In our large series of pharmacoresistent patients with epilepsy (Table), the most frequent histopathologic alterations affected the hippocampus and were characterized by segmental neuronal loss in CA1 and CA4, with the CA2 and dentate gyrus subfields more conserved (i.e., Ammon’s horn sclerosis [9–11]). Dense fibrillary astrogliosis and sclerosis of the tissue are present in all segments with pronounced neuronal cell loss. A second large cohort of patients with epilepsy presents with focal lesions within the neocortex. These lesions usually do not involve the hippocampus proper, and hippocampal cell damage (i.e., segmental cell loss) is absent in most of the surgical specimens (9, 11, 12).

Focal lesions include glioneuronal malformations such as focal cortical dysplasias or low-grade glial and glioneuronal neoplasms such as gangliogliomas and dysembryoplastic neuroepithelial tumors (13–18). Current research efforts address the issue of whether these lesions play an active role in the onset of epileptic seizures or whether perilesional reorganization mechanisms are involved in enhanced seizure susceptibility. Previous studies revealed aberrant expression of neurotransmitter-producing enzymes, neurotransmitter receptors, neuropeptides, and calcium-binding proteins in glioneuronal lesions as well as their adjacent perilesional zone, which is likely to contribute to local hyperexcitability of brain parenchyma (19–21).

Notwithstanding, epilepsy-associated malformations share many clinicopathologic characteristics. Classification systems addressing pathogenetic mechanisms, etiology, and outcome are, therefore, a matter of ongoing debate (13, 22–27). Histopathologic description and grading is a reasonable approach to differentiate specific entities and represents an important stratification parameter for molecular analysis. Histopathologically, glioneuronal lesions present with a variety of cellular and architectural characteristics that substantially differ from common neoplasms of the central nervous system not associated with partial epilepsies and which can be summarized as follows:

• They constitute highly differentiated malformations with benign biologic behavior.
The lesions reveal a distinct histologic appearance (i.e., biphasic composition of highly differentiated glial and potentially dysplastic neuronal components).

- They are generally associated with focal epilepsies.
- The expression of stem cell markers such as the CD34 epitope may point toward a compromised developmental aspect (21, 22).
- Genes with pathogenetic relevance in other brain tumor entities (e.g. p53, EGFR) do not play a role in the molecular pathology of epilepsy-associated malformations (23).

### NEUROPATHOLOGIC ASPECTS OF GLIONEURONAL LESIONS

Circumscribed malformative lesions of the central nervous system comprise a wide spectrum of neuroradiologic and histomorphologic alterations (13, 22–25, 29). The group of malformations of cortical development (MCDs) is clinically as well as histologically diverse and ranges from subtle architectural aberrations to substantial dysplastic lesions with respect to cytologic and structural characteristics. Present classifications of MCDs are based on histologic features, including loss of cortical lamination, glioneuronal and/or neuronal heterotopias, the occurrence of dysplastic or cytomegalic neuronal elements, and so-called “Taylor-type” balloon cells (13, 23, 30). Although the described cytologic and histologic alterations generally relate MCDs to compromised migration and differentiation of neuronal precursors during cortex development (31–33), their pathogenetic relationship and molecular genetic basis are not entirely defined (33, 34). A general differentiation is to be drawn between 1) pure malformations (i.e., lesions with highly differentiated, nonneoplastic glial and potentially dysplastic or immature neuronal components) and 2) tumors with highly differentiated neoplastic glial components and potentially irregularly localized or dysplastic neuronal elements.

### Epilepsy-Associated Tumors

Clinically, glioneuronal tumors commonly manifest with partial seizures. Among a number of different entities, gangliogliomas represent the most frequent neoplasms in surgical specimens from epileptic patients. These tumors account for 5% of brain tumors in childhood, but are rare in adults (21). In a large series of surgical epilepsy specimens obtained during a period of 7 years, gangliogliomas were most frequently encountered within the temporal lobe (35). The dual composition of dysplastic neurons combined with glial cells represents a histopathologic hallmark of gangliogliomas. The neoplastic nature of the tumor is represented by the proliferative and also rarely mitotic activity of the glial cell component, whereas the neuronal tumor element is considered to be nonneoplastic. Nuclear labeling for the proliferating cell nuclear antigen Ki-67 is generally observed exclusively in the astrocytic component (35). The focal nature of gangliogliomas, the differentiated glioneuronal phenotype, and the benign clinical character suggest that they derive from developmentally compromised or dysplastic precursor lesions (21). The stem cell epitope CD34 is abundantly expressed in gangliogliomas (21). By in situ reverse transcription combined with laser microdissection and polymerase chain reaction detection, CD34 expression has been mainly attributed to dysplastic neuronal components in gangliogliomas (21, 36). However, CD34 expression is not restricted to gangliogliomas, but has also been observed within a subpopulation of balloon cells of FCDIIb (22).

A second major entity within the group of glioneuronal tumors is comprised of dysembryoplastic neuroepithelial tumors. These tumors are characterized by so-called “floating neurons” and oligodendrogia-like glial elements (37–39). These findings typify the “simple” variant of the dysembryoplastic neuroepithelial tumors. In contrast, complex tumor variants may also contain glial portions that are similar to pilocytic astrocytomas. Recently, a subtype of epilepsy-associated astrocytoma with a striking monomorphic appearance has been termed “isomorphic variant” and has been related to a particularly long patient survival (40).

### FCDIIb

The wide range of dysplastic and architectural alterations in MCDs and FCDs has been addressed by a variety of clinicopathologic classification systems. Based on distinct clinical and phenotypic features, a frequent subtype has been characterized as focal cortical dysplasia of Taylor’s balloon cell type (FCDIIb) (29). Histopathologically, a glioneuronal malformation with striking similarities to cortical tubers in patients with tuberous sclerosis is present (41). Cortical tubers

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harbor a derangement of the cortical laminar structure (Fig. 1), that is, they manifest as multiple nodules and are microscopically characterized by disruption of the hexalaminar cortical organization, blurring of gray–white matter borders, calcification as well as occurrence of dysplastic neurons, and giant cells similar to balloon cells present in FCD_{Iib} (42).

Despite the strong histomorphologic similarity between epilepsy-associated FCD_{Iib} and cortical tubers, FCD_{Iib} patients generally lack additional manifestations of a neurocutaneous phacomatosis. As a result of the recent progress in magnetic resonance imaging (MRI), malformations of the cerebral cortex can increasingly be recognized during the presurgical evaluation of patients with pharmacoresistant epilepsies. A major advantage of high-resolution MRI is given by the topographic characterization of the lesion concerning size, localization, and extension (28, 43).

**FCD_{Iia} and Architectural Malformations**

In contrast to FCD_{Iib}, FCD_{Iia} lack balloon cells but consist of misshapen, dysplastic neuronal components characterized...
by aberrant orientation, enlarged cell size, and abnormal processes (Fig. 1). Whereas FCD$_{Ib}$ are frequently localized outside the temporal lobe, FCD$_{Ia}$ and gangliogliomas share a preference for temporal localization (13, 14). Also, more subtle variants of MCDs show alterations related to aberrant neuronal migration and differentiation. These lesions comprise white matter neuronal heterotopias (WMNH) and nodular cortical heterotopias (NCH). Also physiologically, ectopic neurons in the white matter are present in the temporal lobe (44). In WMNH associated with pharmacoresistant epilepsy, the number of heterotopic neurons in white matter is substantially increased (44, 45), and small clusters of white matter neurons are found. In contrast, NCH contain clusters of cortical islands in the white matter. These cortical areas lack a regular cortical lamination. FCD$_I$ harbor cortical areas with dyslamination, microcolumnar structure, and individual giant or immature but not dysplastic neurons (13, 46). In addition, ectopic neurons in white matter may be observed in these specimens.

Remarkably, the pathogenetic value for some of the described alterations with respect to epilepsy remains a matter of ongoing debate. In a cohort of temporal lobe tissue of patients with TLE compared with normal autopsy controls, some of the earlier described histopathologic characteristics were found in both patients with TLE and controls (47). This issue may be relevant, particularly in lesions referred to as mild malformations such as heterotopic neurons in cortical lamina I or heterotopic white matter neurons. It should be considered that the occurrence of heterotopic neurons itself is not necessarily pathogenic. Control specimens revealed ectopic white matter neurons in the temporal lobe but only few in extratemporal localization (46). In temporal localization, the number of solitary white matter neurons was shown to be significantly higher in cortical malformative specimens compared with controls (46, 47). Additional histopathologic features significantly associated with TLE specimens comprised clustering of neurons throughout cortical layers II to VI, perivascular clustering of oligodendroglia in the white matter, and the occurrence of glioneuronal hamartias (47). Moreover, a count of more than 10 white matter neurons per high-power field (HPF) was predictive of an inferior postoperative outcome. Such data may suggest that distinct neuropathologic observations are associated with the epileptic process, whereas others appear as normal variants (47).

### MOLECULAR ALTERATIONS IN GLIONEURONAL MALFORMATIONS

Histopathologic similarities between epilepsy-associated circumscribed lesions and central nervous system abnormalities in patients with familial syndromes may suggest that similar molecular pathways are involved in their pathogenesis. Genes with pathogenetic relevance in other brain tumor entities (e.g. p53, EGFR) were not shown to play substantial roles in the molecular pathology of epilepsy-associated malformations (23, 48).

Recent clinicopathologic studies point to a role of genes and pathways in epilepsy-associated glioneuronal lesions (49–51) otherwise associated with rare familial disorders such as TSC (52, 53). TSC is caused by germline mutations of the TSC1 (hamartin) and TSC2 (tuberin) genes on chromosomes 9q and 16p, respectively (54, 55). Tuberous sclerosis complex represents a syndromal disorder characterized by lesions in a variety of tissues, including cortical tubers and subependymal giant cell astrocytomas (World Health Organization [WHO]).

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**FIGURE 1.** Relationship between tuberous sclerosis and epilepsy-associated glioneuronal lesions. (A) Neuronally, a substantial overlap between brain lesions in TSC and epilepsy-associated lesions is present. In tuberous sclerosis, a variety of lesions such as cortical tubers ([A] hematoxylin and eosin [H&E], magnification: 100×, insert magnification: 400×) and subependymal giant cell astrocytomas ([B] H&E, magnification: 100×) is observed. Cortical tubers share aberrant components, i.e. balloon cells and dysplastic neurons with epilepsy-associated malformations such as FCD$_{Ib}$ ([C] H&E, magnification: 100×). Dysplastic neuronal elements are also found in FCD$_{Ia}$ ([E] H&E, magnification: 100×; [F] MAP2 immunohistochemistry, magnification: 100×) and gangliogliomas, which show characteristic satellitosis-like expression of the CD34 stem cell marker ([G] H&E, magnification: 100×; [H] CD34 immunohistochemistry, magnification: 100×). Proliferative activity is only present in gangliogliomas and TSC-associated lesions (e.g. in subependymal giant cell astrocytomas), but not in focal cortical dysplasias. Whereas tuberous sclerosis constitutes an autosomal-dominant familial disorder, epilepsy-associated glioneuronal malformations generally occur sporadically. Substantial differences with respect to magnetic resonance imaging are observed between the different entities: 1) on magnetic resonance imaging, a single cortical tuber cannot be distinguished from an FCD$_{Ib}$ unless it is calcified. Multiple lesions (arrows), however, point to the tuberous sclerosis complex (coronal FLAIR TSE); 2) FCD$_{Ia}$ of the right middle gyrus. A characteristic hallmark is a hyperintense signal tapering toward the lateral ventricle (horizontal arrow); axial FLAIR TSE magnetic resonance image); 3) in FCD$_{Ib}$, a wide spectrum of neuroradiologic alterations is observed. By planar brain surface reformation, irregular gray matter appearance of the insular cortex could be demonstrated; and 4) ganglioglioma of the right middle temporal gyrus. Coronal T2-weighted TSE magnetic resonance image. Note the different components of the ganglioglioma consisting of slightly hyperintense and broadened cortex (horizontal arrow). (B) Comparison of allelic variants in different epilepsy-associated glioneuronal lesions. Whereas FCD$_{Ia}$ show an accumulation of partially coding polymorphisms in TSC1, FCD$_{Ib}$ and gangliogliomas exhibit increased incidences of polymorphisms in TSC2. The differential patterns of allelic variants in TSC1 and TSC2 point to FCD$_{Ia}$ and FCD$_{Ib}$ as distinct entities and strongly argue against FCD$_{Ib}$ as a dysplastic precursor lesion for gangliogliomas. The somatic mutation of TSC2 Intron 32 was restricted to glial cellular elements of a ganglioglioma and was compatible with a clonal expansion of the glial component within this tumor. (FCD$_{Ia}$: n = 48, FCD$_{Ib}$: n = 20, gangliogliomas: n = 20; polymorphisms shown in color as follows: FCD$_{Ia}$ in red; FCD$_{Ib}$ in yellow; ganglioglioma in blue; and mutation in black) (16, 51, 60).
grade I) in the brain, facial angiofibromata, or fibroma of the skin and angiomylipoma of the kidney (56). Hamartin and tuberin form a tumor-suppressor complex and play a central role in the phosphatidylinositol 3-kinase (PI3K)/mTOR pathway, which is involved in morphogenesis, cell adhesion/migration, and cell fate determination (49, 57, 58). However, patients with epilepsy with gangliogliomas or FCDs do not usually present with additional TSC-associated stigmata as mentioned previously (56). Recently, an anaplastic ganglioglioma was detected in the Eker mutant rat known to harbor genetic alterations of the TSC2 (59).

To analyze a potential pathogenetic role of TSC1/TSC2 in epilepsy-associated glioneuronal lesions, we have examined whether aberrant patterns of allelic variants in these genes occur in sporadic FCDIIb (51), gangliogliomas (16), as well as FCDIIa, WMNH, and NCH lesions (60). In a cohort of 48 FCDIIb cases, two thirds of the specimens revealed sequence alterations in the TSC1 gene. Two sequence alterations affecting exons 5 and 17 resulted in amino acid exchange of the TSC1 gene. Intriguingly, the base transition in exon 17 (2415C>T; His732Tyr), a complex exon 14/intron 13 polymorphism as well as a silent polymorphism in exon 22 of TSC1 (3050C>T; 943A Ala), were all significantly increased in FCDIIb compared with controls (Fig. 1) (61–63). The base exchange in exon 17 is located in the interaction domain of hamartin with tuberin, suggesting a potentially compromised tumor-suppressor function of the resulting protein (53). Moreover, 11 of 15 FCDIIb specimens that were subjected to loss of heterozygosity (LOH) analysis at the TSC1 locus revealed LOH in the chromosomal region 9q34 of TSC1 in multiple microsatellite markers. Chromosomal instability in FCDIIb was observed mainly at the 9q area but not at other localizations of the genome (64). With respect to the two-hit hypothesis for the inactivation of tumor-suppressor genes (i.e. LOH and associated mutation in the second allele [65]), these findings have certain implications. The observed combinations of LOH at the TSC1 locus and sequence polymorphisms in the second allele suggest that the latter may act as a predisposing germline variant with low penetrance and a rather restricted manifestation pattern. In light of the increasing information on hamartin and tuberin as a cell cycle-regulating complex (66, 67), such variant alleles may induce proliferation activity only for a short time during brain development. In contrast to the findings in TSC1, none of the few observed TSC2 alterations were significantly increased in FCDIIb compared with controls (16, 68–71).

Unlike FCDIIb, mutational analysis in 20 ganglioglioma specimens revealed abundant sequence alterations in the TSC2 gene (16). An intronic polymorphism in intron 4 of TSC2 was substantially increased in gangliogliomas compared with controls (16, 72). The same was true for a silent polymorphism located in exon 40 (16). In contrast to FCDIIb, no polymorphisms in TSC1 were substantially increased in gangliogliomas (16). In particular, the exon 17 polymorphism frequently encountered in FCDIIb was not observed in gangliogliomas. In a ganglioglioma, a sequence alteration observed in intron 32 represented a somatic mutation (Fig. 1). Subsequent laser-capture microdissection of glial and dysplastic neuronal components demonstrated the mutation to be restricted to the glial cell component. This observation pointed toward a clonal origin of the glial tumor component in this case. The finding is compatible with the hypothesis that gangliogliomas develop from a dysplastic precursor lesion by neoplastic transformation of the glial component.

All sequence alterations present in FCDIIa had been previously described as polymorphisms and were found either in gangliogliomas and/or FCDIIb (16, 51, 55, 72). Intriguingly, in FCDIIa, abundant genomic polymorphisms were detected in intron 4 of TSC2, but no allelic variants in exon 17 of TSC1 were observed (60). With respect to LOH at the genomic TSC1 locus (51, 64), LOH was not found to be a prominent alteration in FCDIIa. This also is in contrast to FCDIIb, in which LOH of the TSC1 locus were frequently observed (51).

FCDI and WMNH shared abundant polymorphisms in intron 13/exon 14 of TSC1, which had been previously reported to be significantly increased in FCDIIb (51). On the other hand, they differed from FCDIIb by lack of significantly increased frequencies of polymorphisms in exon 17 and 22 of TSC1. Furthermore, FCDI and WMNH did not harbor substantial genomic sequence alterations of TSC2. NCH samples had no significant sequence alterations in TSC1 or TSC2. These data showed variable patterns of allelic variants in this group of milder cortical malformations (60).

Overlap in allelic distribution patterns between entities can suggest common pathogenetic mechanisms and may support recent clinicopathologic classification systems (13, 24, 25). Whereas significantly increased genomic polymorphisms for TSC1 are present in FCDIIb (51), accumulation of allelic variants only of TSC2 is found in FCDIIa samples (Fig. 1). The coding polymorphism in exon 17 of TSC1 appears as a most pronounced classifier between FCDIIb and FCDIIa patients. The data argue in favor of the concept that different pathogenetic events occur at least in FCDIIb and FCDIIa. Also, clinical observations with respect to a favorable postsurgical outcome in FCDIIb patients support this idea (28). Matching allelic variant patterns of TSC2 may be suggestive for a role of FCDIIa as a potential dysplastic precursor lesion for gangliogliomas (21). However, coexistence or transition of FCDIIa to gangliogliomas have been rarely described in biopsy specimens of patients with epilepsy (unpublished observation in 418 gangliogliomas, in which only 3 cases revealed distinct signs of cortical dysplasia; www.epilepsie-register.de; see also [73]).

ALTERATIONS OF THE PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) PATHWAY IN GLIONEURAL MALFORMATIONS

Recent data have suggested that hamartin and tuberin constitute a tumor-suppressor mechanism (74), which plays a central role in the insulin/PI3K signaling pathway (58, 75). The PI3K pathway is critical for cell size and growth control as well as cortical development and neuronal migration (66, 67). Binding of insulin to its membrane receptor activates the cascade components PI3K, Akt, TSC1/TSC2, mTOR (mammalian target of rapamycin), as well as the transcription factors p70S6 kinase (S6K) and ribosomal S6 protein (S6) (76, 77).
Inactivation of the TSC1/TSC2 complex by phosphorylation through Akt results in phosphorylation of mTOR and subsequent activation of the mentioned transcription factors interfering with cell size control (78–82). In giant cells in cortical tubers with mutations in TSC1 or TSC2, inhibition of the PI3K pathway appears compromised and results in extensive pathway activation downstream of the ablated tumor-suppressor mechanism, namely increased detection of phospho-S6, phospho-S6K and its targets phospho-STAT3 and phospho-4EBP1 (49, 50). In contrast, just individual PI3K-pathway downstream components have been recently reported to be activated in FCDIIb, i.e. the eukaryotic translation initiation factor (elf) 4G and phospho-S6 (49, 50), suggesting differential PI3K pathway activation in cortical tubers and FCDIIb. These intriguing data suggest that activated S6 protein is present in FCDIIb components, although S6K is not phosphorylated in the same cells (49, 50). The origin of the signal for phosphorylation of S6 in FCDIIb currently remains enigmatic (49, 50). It will be an important task for future studies to characterize the signal donor for phosphorylation of S6.

Hamartin and tuberin direct cellular differentiation, migration, cell cycle, and size by interaction with a number of different molecules (58, 75). Tuberin includes a region homologous to the GTPase-activating protein (GAP) for the small-molecular-weight GTPase Rap1 (Fig. 1) (55). A rabaptin-5 binding domain has been reported in the vicinity of the GAP-related domain at the C-terminal region of tuberin (83). A tuberin–rabaptin-5 complex is involved in the regulation of endocytosis (83). The Drosophila homolog of TSC2, giant, was found to be required to enter the M and S phase of the cell cycle (75). Tuberin is localized at the Golgi apparatus/perinuclear area consistent with a potential role for protein trafficking (84, 85). Hamartin binds to ezrin/radixin/moesin (ERM) proteins, suggesting a functional link to Rho GTPases, actin-based cytoskeletal components, and cell-adhesion processes (86). Recent data show aberrant accumulation of ERM proteins in dysplastic neuronal components in a variety of glioneuronal lesions as well as in balloon cells in FCDIIb (87). Furthermore, interaction of tuberin and hamartin with CDK1 and cyclin B1 as well as of tuberin with cyclin B1 have been reported compatible with an important role of the hamartin/tuberin complex in cell-cycle control (88). The pathogenic relevance of distinct PI3K-pathway alterations has to be precisely addressed in the future.

ALTERATIONS OF THE REELIN PATHWAY IN GLIONEURONAL MALFORMATIONS

Another major signal pathway for neuronal development, modification of the cytoskeleton and cellular migration processes, is the reelin signal transduction cascade (89–91). Key effector components of the reelin pathway are doublecortin (DCX) as well as cyclin-dependent kinase 5 (CDK5), p35, and disabled-1 (dab1). DCX exhibits considerable sequence homologies to the Ca++/calmodulin-dependent kinase, suggesting Ca++-dependent/activated mechanisms as a major factor for neuronal migration (92). DCX is expressed at high levels in the fetal central nervous system, and perturbation of DCX function in vitro results in interruption of microtubuli. Thereby, the cellular shape and cytoskeletal function as well as cell migration are compromised in vivo (93–95). The double cortex syndrome represents a specific neuronal migration disorders caused by inactivating mutations of the DCX gene (96) and is clinically characterized by seizures, cognitive dysfunction, and neurologic deficits.

The CDK5 gene is also involved in appropriate differentiation of neuronal cells. It is specifically expressed in postmitotic neurons and muscle cells and its function is important during the transition from G- to S-phase of the cell cycle (97). CDK5 ablation in mice results in compromised central nervous system architecture by migration defects (98–100). Functional loss of CDK5 results in impairment of neuronal migration and differentiation (99–101). Alterations of CDK5 have been reported in cortical malformations (102).

CDK5 and its activator-protein p35 are essential for microtubule assembly (103) and cell-cycle control (104, 105). The cdk5/p35 complex constitutes a serine/threonine kinase system operating primarily in postmitotic neurons and during later stages of cortical development in the human brain (103). In mice lacking p35, severe cortical dyslamination can be observed (101). Signals for cdk5/p35 are transduced by dab1, a cytoplasmic kinase. Binding of reelin to the plasma membrane ApoE receptor results in dab1 phosphorylation (106). Cdk5/p35 and reelin/dab1 have recently been shown to act synergistically in neuronal migration and differentiation processes (107).

Potential alterations on the DNA and expression level of CDK5, DCX, p35, and dab1 have been therefore addressed in gangliogliomas (16, 108). No mutations of the genes were observed in the series of gangliogliomas (17, 109). In contrast, lower mRNA expression of the CDK5, DCX, p35, and dab1 genes was present in gangliogliomas compared with normal central nervous system tissue controls matched for grey/white matter (Fig. 2) (16, 108). Although mutational analysis of CDK5, DCX, p35, and dab1 revealed no sequence alterations in a series of gangliogliomas, compromised reelin signaling represents a potential mechanism for glioneuronal maldevelopment and/or precursor lesions underlying neoplastic transformation. Impaired function of more than a single molecule of the reelin-signaling cascade has been shown to act in a synergistically negative effect on positioning of cortical neurons in the developing mouse brain (100).

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activity can produce significantly altered morphologic phenotypes in experimental models of focal epilepsies (109). Another important objective will be the functional analysis of identified pathogens. Optimized animal models of focal cortical malformations are also required to address molecular mechanisms of epileptogenesis and pharmacoresistance. It is tempting to speculate that comprehensive analysis of clinical, imaging, neuropathologic, and molecular findings will be mandatory to introduce novel classification systems and refined therapeutic strategies in patients with focal epilepsies and glioneuronal malformations.

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