Genetic alterations in uncommon low-grade neuroepithelial tumors: *BRAF*, *FGFR1*, and *MYB* mutations occur at high frequency and align with morphology

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Abstract

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Low-grade neuroepithelial tumors (LGNTs) are diverse CNS tumors presenting in children and young adults, often with a history of epilepsy. While the genetic profiles of common LGNTs, such as the pilocytic astrocytoma and 'adult-type' diffuse gliomas, are largely established, those of uncommon LGNTs remain to be defined.

In this study, we have used massively parallel sequencing and various targeted molecular genetic approaches to study alterations in 91 LGNTs, mostly from children but including young adult patients. These tumors comprise dysembryoplastic neuroepithelial tumors (DNETs; n=22), diffuse oligodendroglial tumors (d-OTs; n=20), diffuse astrocytomas (DAs; n=17), angiocentric gliomas (n=15), and gangliogliomas (n=17).

Most LGNTs (84%) analyzed by whole-genome sequencing (WGS) were characterized by a single driver genetic alteration. Alterations of *FGFR1* occurred frequently in LGNTs composed of oligodendrocyte-like cells, being present in 82% of DNETs and 40% of d-OTs. In contrast, a *MYB-QKI* fusion characterized almost all angiocentric gliomas (87%), and *MYB* fusion genes were the most common genetic alteration in DAs (41%). A BRAF:p.V600E mutation was present in 35% of gangliogliomas and 18% of DAs. Pathogenic alterations in *FGFR1/2/3*, *BRAF*, or *MYB/MYBL1* occurred in 78% of the series. Adult-type d-OTs with an *IDH1/2* mutation occurred in four adolescents, the youngest aged 15 years at biopsy. Despite a detailed analysis, novel genetic alterations were limited to two fusion genes, *EWSR1-PATZ1* and *SLMAP-NTRK2*, both in gangliogliomas.

Alterations in BRAF, FGFR1, or MYB account for most pathogenic alterations in LGNTs, including pilocytic astrocytomas, and alignment of these genetic alterations and cytologic features across LGNTs has diagnostic implications. Additionally, therapeutic options based upon targeting the effects of these alterations are already in clinical trials.

Introduction

Low-grade gliomas (LGGs) and low-grade glioneuronal tumors, together designated 'low-grade neuroepithelial tumors' (LGNTs), represent an important group of central nervous system (CNS) neoplasms in children and young adults [34]. LGNTs include the pilocytic astrocytoma, the commonest pediatric brain tumor, but encompass a large variety of uncommon CNS tumors, some of which – ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), angiocentric glioma – are associated with a history of chronic epilepsy and are referred to as 'long-term epilepsy-associated tumors' (LEATs) [7,59].

Overall survival among the broad category of LGNTs is good, largely because many pilocytic astrocytomas are circumscribed non-infiltrative tumors and present at anatomic sites that make them amenable to surgical resection, such as the cerebellar hemisphere [4,17]. However, a significant proportion of less common LGNTs diffusely infiltrates the CNS or presents at a site where surgical resection is not feasible without significantly damaging the patient. Such tumors cause premature death, following a prolonged period of

increasing morbidity that exacts a significant economic and emotional toll on families and health care providers [57].

Over the past decade, our understanding of genetic alterations in pediatric LGNTs has increased significantly, beyond recognition of the association between neurofibromatosis type 1 (NF1) and optic pathway glioma [2,24,45]. The *NF1* gene product, neurofibromin 1, is a negative regulator of the MAPK pathway, and recurrent genetic alterations in other members of this pathway have been discovered in multiple types of LGNT [25,67]. However, genetic alterations in various uncommon types of LGNT, particularly some LEATs, have not been studied in a systematic manner.

We report a study of genetic alterations in a series of 91 uncommon LGNTs from children and young adults, which consists of diffuse astrocytomas (DAs), dysembryoplastic neuroepithelial tumors (DNETs), oligodendrogliomas, oligoastrocytomas, angiocentric gliomas (AGs), and gangliogliomas. Our analysis demonstrates a limited repertoire of recurrent genetic alterations that align strongly with morphology.

Methods

Sample series and processing

The study cohort comprised 91 primary cerebral LGNTs (Supp. Table S1), presenting in 48 (53%) male and 43 (47%) female patients, with a median age at surgery of 10 years (range 1 – 41 years). Three broad categories of LGNT were represented: (i) tumors with a dominant oligodendroglial phenotype – dysembryoplastic neuroepithelial tumors (DNETs, n=22) and the diffuse oligodendroglial tumors (d-OTs, n=20), oligodendrogliomas and oligoastrocytomas, (ii) tumors with a dominant astrocytic phenotype – angiocentric gliomas (AGs, n=15) and diffuse astrocytomas (DAs, n=17), and (iii) gangliogliomas (n=17). The histopathological diagnosis was reviewed in each case (DWE). Fifty-nine samples were snap-frozen at the time of first resection. Thirty-two samples were available only as archived formalin-fixed paraffin wax-embedded (FFPE) material. Tumor and germline blood samples were processed according to starting material and as previously described (see Supplemental Methods & Supp. Fig. S1) [22,67].

Whole genome, whole exome and transcriptome sequencing and data analysis

Whole genome, whole exome, and transcriptome sequencing (WGS, WES, RNA-seq) were undertaken using derivatives from frozen samples as previously described [65,66]. WGS and WES mapping, coverage and quality assessment, single nucleotide variation (SNV) and insertion/deletion (indel) detection, tier annotation for sequence mutations, prediction of the deleterious effects of missense mutations, structural variant (SV) detection, and identification of loss of heterozygosity (LOH) have been described previously [65,66]. The reference human genome assembly NCBI Build 37 was used to map all samples. Mapping statistics and coverage for each sample on different sequencing platforms are summarized in the supplemental methods/analysis and Supp. Table S2.

Mutation hotspot analysis by Sanger sequencing

Mutational hotspots in *BRAF*, *KRAS*, *IDH1*, *IDH2* and *H3F3A* were sequenced in gDNA from the entire series of tumors using previously published primers [22,58,62]. Point mutations within *FGFR1* and *FGFR3* were sequenced using primer pairs listed in Supp. Table S3. Amplicons were generated using GoTaq™ DNA Polymerase (Promega, Madison, WI), and PCR products were sequenced using BigDye version 3.1 chemistry and a 3730XL DNA analyzer (Applied Biosystems, Foster City, CA). Output data were analyzed using CLC Main Workbench sequence analysis software version 6.0.2 (CLC bio, Cambridge, MA).

Genome-wide copy number analysis and clustering analysis by DNA methylation profiling

Genome-wide DNA methylation profiles were generated for 89 tumor samples, using the Illumina Infinium HumanMethylation450 BeadChip array. Frozen and FFPE-derived genomic DNA (500ng) was bisulfite-treated using the Zymo EZ DNA Methylation Kit according to the following thermocycling conditions (16 cycles: 95°C for 30sec, 50°C for 1hr). Following bisulfite treatment, DNA samples were desulphonated, column purified, then eluted using 12μl of elution buffer (Zymo Research). FFPE-derived DNA samples were then processed using the Illumina Infinium HD FFPE Restore kit according to the manufacturer's protocol. All bisulfite-converted DNA (frozen) and bisulfite-converted and restored DNA (FFPE) samples were processed using the Illumina Infinium Methylation Assay, including hybridization to HumanMethylation450 BeadChips, single base extension assay, staining and scanning using the Illumina HiScan system, according to manufacturer's recommendations. Data were preprocessed using the SWAN normalization method in R package *minfi* to normalize Type I and Type II probe bias. The combined intensity values of the methylation probes were then analyzed using R package *conumee* to generate genome-wide DNA copy number profiles. For unsupervised hierarchical clustering analysis, the following additional filters were applied: (i) removal of probes targeting X and Y chromosomes, (ii) removal of probes with CpG-sites overlapping a single nucleotide polymorphism (dbSNP138), and (iii) removal of probes with detection p-value>0.05 in more than 5% of the samples. Beta values were calculated, and the top 5% most variable methylated CpG probes as measured by median absolute deviation were selected. Tumor samples were clustered by applying a "ward" method on euclidean distance.

Interphase fluorescence in situ hybridizaton (iFISH)

Dual-color iFISH was performed on 4μm FFPE tissue sections, as previously described [20]. BAC clones (BACPAC Resources, Oakland, CA) used to develop both break-apart and copy number iFISH probe sets are detailed in Supp. Table S4.

URLs

NCBI RefSeq, http://www.ncbi.nlm.nih.gov/refseq/; NCBI reference human genome, http://www.ncbi.nlm.nih.gov/genome/51; National Heart, Lung, and Blood Institute GO Exome Sequencing Project (ESP), http://evs.gs.washington.edu/EVS/.

Accession codes

Our entire genomic data set, including whole-genome sequencing, whole-exome sequencing and RNA-seq has been deposited at the European Bioinformatics Institute (EBI) under accession number EGAS00001000255.

Results

NGS overview

A total of 1,047 somatic sequence mutations, including only 28 non-silent coding mutations (Supp. Table S5), and 47 SVs (Supp. Table S6) were identified by WGS of 19 LGNTs (Supp. Fig. 2). In addition, 72 somatic mutations (38 non-silent) were found by WES (Supp. Table S7). Transcriptome sequencing captured 77 SVs (Supp. Table S8). The background mutation rate derived from SNVs in non-repetitive regions in tumors analyzed by WGS ranged from 8.05×10^{-10} to 2.66×10^{-7} mutations per base, with an average mutation rate of 4.39×10^{-8} mutations per base (Supp. Table S9). Overall, LGNTs showed a median of 1 non-silent somatic mutation per case (range 0–7); and the cohort showed a median of 1 SV per case (range 0–14). Despite the paucity of genetic alterations overall, we found multiple recurrent abnormalities in different LGNT subtypes.

Eighty-nine percent (55/62) NGS cases had at least 1 recurrent abnormality involving *FGFR1/FGFR3*, *MYB/MYBL1*, *BRAF*, *PDGFRA*, *NF1*, and *NTRK2* (Supp. Table S10). Sixty one percent (38/62) of NGS cases contained an SV, consistent with our previous observation that SVs are frequent driver events in LGNTs [67]. Four cases were found to contain multiple driver abnormalities: LGNT57 contained mutations within *FGFR1* and *BRAF*, and LGNT58 contained mutations within *FGFR1*, *KRAS* and *NF1*, and LGNT69 and LGNT63 contained both a *MYB-QKI* gene fusion and a BRAF:p.V600E mutation (Supp. Table S10).

Different sequencing strategies revealed recurrent genetic alterations in all types of LGNT. These alterations were dominated by SNVs, SVs, or tyrosine kinase domain (TKD) duplications in *FGFR1* (33% of tumors), SVs involving *MYB* (22%), and *BRAF* fusions or mutations (18%), mainly BRAF:p.V600E. Each of these principal genetic alterations was associated with a morphological phenotype. *FGFR1* abnormalities were greatly enriched in LGNTs with an oligodendroglial phenotype – dysembryoplastic neuroepithelial tumors (DNETs) and the diffuse oligodendroglial tumors (d-OTs), while practically all *MYB* abnormalities were detected in angiocentric gliomas and diffuse astrocytomas, and *BRAF* alterations were most frequent among gangliogliomas.

FGFR1 alterations in cerebral LGNTs with oligodendroglial phenotype

Genetic alterations were detected in 39/42 (93%) of LGNTs with an oligodendroglial phenotype – DNETs and d-OTs (Fig. 1). *FGFR1* alterations were detected in 26/42 (62%) and comprised SNVs, TKD duplications, and fusions. Pathogenic *FGFR1* SNVs, which were single or 'doublet' missense mutations in the TKD, occurred only in DNETs or d-OTs across the LGNT series. Doublet missense mutations occurred on the same allele within 1–9 codons of each other (Fig. 1, Supp. Fig. 3). In LGNT34, two *FGFR1* mutations (N544K &

R659L) were identified on different alleles. Most (14/17; 82%) FGFR1 TKD duplications were detected among DNETs or d-OTs; only two were in diffuse astrocytomas and one occurred in a ganglioglioma (Supp. Fig. 4). Three of five FGFR1 fusions, all *FGFR1-TACC1*, were detected in DNETs or d-OTs; two others, one *FGFR1-TACC1* and one *FGFR3-TACC3*, occurred in diffuse astrocytomas.

Other pathogenic alterations occurred at low frequency in DNETs and d-OTs: two CNAs in *FGFR2* (5%), two *PDGFRA* mutations (5%), one BRAF:p.V600E (2%), one BRAF:p.G503>GVLR (2%), one *BRAF-RNF130* (2%), one *NAV1-NTRK2* (2%), and one *MYB-MAML2* (2%). Four dOTs harbored an *IDH1/2* mutation and other genetic alterations characteristic of 'adult-type' diffuse grade II oligodendrogliomas. These tumors occurred in teenagers and young adults aged 15–22 years at diagnosis. No alteration was found in three LGNTs with an oligodendroglial phenotype.

All *FGFR1* SNVs occurred in DNETs, with one exception, an oligoastrocytoma that had an FGFR1:p.N544K mutation and concurrent NF1:p.T653fs and KRAS:p.G12D mutations. Tumors with an *FGFR1* SNV presented at an older mean age, 14.2 years, than those with an *FGFR1* TKD duplication, 7.4 years (p=0.0002), though this partly reflects a higher mean age at presentation among patients with DNET, 12.4 years, than those with d-OTs, 9.2 (p=0.036). No association between any genetic alteration and tumor location was evident.

MYB alterations in cerebral LGNTs with astrocytic phenotype

Pathogenic alterations were detected in 31/32 (97%) of LGNTs with an astrocytic morphology – diffuse astrocytomas and angiocentric gliomas (Fig. 2), and the dominant lesions were *MYB* fusions (21/32; 66%). All angiocentric gliomas harbored a *MYB-QKI* fusion (13/15; 87%), *MYB-ESR1* fusion (1/15), or *QKI* rearrangement (1/15) (Supp. Figs. 5, 6). The last of these had no apparent involvement of *MYB* or *MYBL1*, showing only split signals with iFISH break-apart probes across *QKI*. We did not have sufficient derivatives from this tumor for FFPE RNA-seq, so were unable to determine whether a cryptic *MYB-QKI* aberration was present in this case, or whether *QKI* was fused to another gene partner. Most *MYB-QKI* fusions (78%) were between *MYB* exon 15 and *QKI* exon 5. Fusions were also identified between *MYB* exon 9 and *QKI* exon 5 (Supp. Fig. S5). Two tumors with a *MYB-QKI* fusion also harbored a BRAF:p.V600E mutation (Supp. Fig. S7).

Diffuse astrocytomas were more heterogeneous. *MYB* or *MYBL1* rearrangements were detected in 7/17 tumors (41%), while *BRAF* or *FGFR1/3* alterations were present in 4 tumors each (Fig. 2, Supp. Fig. S7). One tumor had an H3F3A:p.K27M mutation, which we have reported before [67]. Another tumor harbored only an *ELAC2* duplication of uncertain significance, although variants in this gene have been implicated in susceptibility to hereditary prostatic cancer [1].

Only one other tumor across the series, an oligodendroglioma with a *MYB-MAML2* fusion, harbored a *MYB* or *MYBL1* alteration. Among diffuse astrocytomas, there was no obvious difference in radiological characteristics, including anatomic site, or outcome between those tumors with *MYB*, those with *MYBL1* alterations, and those with other genetic alterations (data not shown).

BRAF alterations in gangliogliomas

WGS, WES, or RNA-seq was undertaken on 15/17 (88%) gangliogliomas, but in two of these fifteen (13%) no significant alteration was detected (Supp. Fig. S7). Otherwise, abnormalities in gangliogliomas most frequently involved *BRAF* (9/17; 53%), specifically a BRAF:p.V600E mutation in 6/17 tumors (35%), and a *MACF1-BRAF*, *AGK-BRAF*, or *GNAI1-BRAF* fusion in each of three others (Fig. 3). All of these alterations are predicted to activate the downstream effects of BRAF in a constitutive manner. Individual gangliogliomas contained single miscellaneous pathogenic alterations: *NF1* SNV, *FGFR1* TKD duplication, and an *EWSR1-PATZ1* or *SLMAP-NTRK2* fusion (Fig. 3). No particular clinicopathological associations were found for these diverse genetic abnormalities.

LGNT methylation profiling

Hierarchical clustering analysis of the DNA methylation profiles of 71 LGNTs with *FGFR1*, *MYB/MYBL1*, *BRAF*, or *IDH1/2* alterations segregated tumors primarily by genetic alteration (Fig. 4), although the strong association between genetic alteration and morphology was also apparent. Principal component analysis of these data demonstrated clear separation of the four genetic subgroups, consistent with the results from hierarchical clustering (Fig. 4b). A similar analysis including the entire study cohort showed a similar result and allowed review of the assignment of those tumors for which no genetic alteration was discovered (Supp. Fig. S8). Of six such tumors, two gangliogliomas segregated with most other gangliogliomas in a genetic group characterized mainly by *BRAF* alterations, while a DNET and oligodendroglioma were placed among tumors with *FGFR1* alterations.

Copy number alterations among LGNTs

Very few CNAs were discovered among the series of LGNTs using the Illumina methylation array or Affymetrix SNP 6.0 platforms (Supp. Fig. S9). Recurrent changes included 1p/19q codeletion among the four adult-type d-OTs, and gains of chromosomes 5, 7, and 12 were found among disparate LGNTs with a various genetic alterations. Focal deletions at 6q23, involving the 3′ terminal region of *MYB* and the 5′ region of *QKI* were seen in 4 angiocentric gliomas, as previously reported [58]. However, the majority of angiocentric gliomas with confirmed *MYB-QKI* fusions did not display CNAs at these loci. No other recurrent focal CNA was identified.

Discussion

The present study extends our earlier WGS analysis of low-grade gliomas by focusing on uncommon LGNTs [67], including several LEATs – DNETs, angiocentric gliomas, and gangliogliomas. In addition, we have increased the number of 'pediatric-type' WHO grade II diffuse LGGs analyzed on NGS platforms, both astrocytomas and d-OTs. WGS has consistently shown that pediatric LGGs contain only one pathogenic alteration, and this principle extends to most of the uncommon LGNTs; 84% of the present series analyzed by WGS had just a single SNV or SV in a known oncogene. Combinations of common genetic alterations did occur in a few tumors from the series, including an oligoastrocytoma with pathogenic *FGFR1*, *KRAS*, and *NF1* mutations and two angiocentric gliomas with a MYB-QKI fusion and BRAF:p.V600E mutation. Very few novel genetic alterations were

discovered in our study. Instead, *FGFR1*, *MYB*, and *BRAF* alterations dominated our series of LGNTs and showed clear alignment with tumor morphology.

LGNTs with an oligodendroglial phenotype and composed primarily of oligodendrocyte-like cells (OLCs) were characterized by recurrent *FGFR1* alterations. OLCs dominate the histopathology of DNETs and the diffuse oligodendroglial tumors (d-OTs), oligodendroglioma and oligoastrocytoma. While d-OTs are diffuse tumors and DNETs are generally nodular tumors, overlap between their architectural, as well as cytologic, features can occur; DNETs sometimes demonstrate a diffuse element, in which OLCs invade the cortex and subcortical white matter to resemble an oligodendroglioma [14,6]. *FGFR1* alterations in this axis of tumors encompassed TKD duplications, fusion genes, and mutations within the TKD, all of which have been reported before in diverse tumor types of varying malignancy, including LGGs, malignant melanoma, and glioblastoma [5,31,48,67], though *FGFR1* amplification is a more common alteration in several types of carcinoma, including lung, breast, and bladder [41,49,50]. Such alterations result in constitutively activated signaling pathways downstream of FGFR1 [55,67]. Published studies of genetic alterations in DNETs are limited, focusing on *BRAF*, rather then *FGFR1* [10,43,51]. These find *BRAF* alterations at a higher frequency than in our dataset (Table 1). Aside from those in our earlier publication [67], there are no data on pediatric d-OTs.

With the exception of a single oligoastrocytoma, *FGFR1* SNVs occurred only in DNETs, and pathogenic *FGFR1* alterations, including TKD duplications, dominated these tumors, occurring in 82%. In contrast, d-OTs mainly harbored *FGFR1* TKD duplications, rather than SNVs, and were more heterogeneous, with *FGFR2*, *PDGFRA*, *BRAF*, and single *NTRK* and *MYB* alterations. These genetic alterations would be predicted to have similar effects on the MAPK and PI3K pathways as the recurrent *FGFR1* alterations [30,67]. In 4/8 DNETs with *FGFR1* SNVs, 'doublet' missense *FGFR1* mutations were located 1–9 codons apart on the same allele (Fig. 1). Similar 'doublet' mutations have been recorded in other genes, such as *KRAS* in pilocytic astrocytoma or *EGFR* in lung carcinoma [16,25], but the mechanistic basis of any selective advantage that 'doublet' *FGFR1* mutations might have is unknown. No *FGFR2/3* activating mutations were identified in this study cohort; *FGFR2* CNAs were seen, but were rare findings in just 2% of cases.

Our series of 15 angiocentric gliomas largely comprised tumors for which only FFPE-derived material was available, so it was not possible to gain a comprehensive insight into the genomic landscape of these tumors. However, our data show that nearly all angiocentric gliomas contain a *MYB-QKI* fusion. Other partner genes for *MYB* appear to be rare in this tumor. In contrast, the histologically related DAs appear more heterogeneous; some tumors harbor *MYB* or *MYBL1* fusions or CNAs, while others show mutations or SVs of *BRAF* or TKD duplication or SVs of *FGFR1*. These findings for two types of LGNT with a predominantly astrocytic phenotype mirror our findings for LGNTs with an oligodendroglial phenotype – on each axis, diffuse WHO grade II gliomas are more heterogeneous than the more circumscribed WHO grade I tumors (Fig. 5).

MYB has a long history as a proto-oncogene, but has so far been implicated in the oncogenesis of few tumors [47,56]. *MYB* duplications and balanced reciprocal t(6;7)

(q23;q34) translocations between the regulatory sequence for the T-cell receptor-beta gene and *MYB* have been demonstrated in some patients with T-ALL, and high-level amplifications have been found in one third of hereditary (*BRAC1*) breast cancers [27,11,29]. A translocation between *MYB* and the nuclear transcription factor *NFIB* has been detected in approximately 30% of adenoid cystic carcinomas from the breast or salivary glands [42]. The rearrangement removes the final exon and 3′UTR of *MYB*. The 3′UTR contains binding sites for several microRNAs (miR-15a, miR-16-1, and miR-150) that negatively regulate *MYB* transcription; *MYB* overexpression at the RNA and protein levels results from the loss of this regulatory site. *MYB-QKI* rearrangements in AGs that fuse exon 15 of *MYB* with exon 5 of *QKI* also remove this 3′UTR regulatory site, while the fusion between *MYB* exon 9 and *QKI* exon 5 in LGNT62 and LGNT71 also removes the entire inhibitory C-terminal domain of *MYB* (Supp. Fig. S5). Other mechanisms that increase expression of *MYB*, which we have previously demonstrated at the protein level in AGs and diffuse LGGs, are amplification and fusions with other gene partners [58,67].

QKI is a member of the highly conserved signal transduction and activator of RNA (STAR) family of RNA-binding proteins and has a role in myelination through the regulation of differentiation in oligodendrocytes and Schwann cells [21]. Nuclear QKI levels decline throughout CNS maturation, while intracytoplasmic forms rise during myelination. In AGs, *MYB* fuses to exon 5 of *QKI*, which means that the KH domain responsible for RNA-binding is lost. However, it is possible that the C-terminal domain of QKI influences the location and activity of MYB, enhancing its oncogenic activities.

Angiocentric gliomas have an astrocytic morphology, but also demonstrate features of ependymal differentiation, which manifests as a distinctive punctate intracytoplasmic immunoreactivity for EMA and extracellular cilia, microvilli-containing lumens, and zonulae adherentes at the ultrastructural level [44,61]. However, our data demonstrate that angiocentric gliomas harbor alterations that are found in pediatric-type low-grade astrocytomas, rather than ependymomas. Most pediatric supratentorial ependymomas harbor a characteristic *C11orf95-RELA* fusion [38], but this SV was not found in any angiocentric glioma from the present series. In addition, we have analyzed two large cerebral ependymomas with an infiltrative subcortical component that resembled the phenotype of angiocentric glioma (Suppl Fig. S10). Both of these tumors, which were not included among LGNTs in the present series, demonstrated an iFISH profile consistent with the presence of a *C11orf95-RELA* fusion, but no alteration in *MYB* or *QKI*.

The ganglioglioma is a low-grade glioneuronal tumor composed of large dystrophic neuronal cells and a glial element that generally resembles a pilocytic astrocytoma or diffuse astrocytoma. The latter may infiltrate surrounding CNS parenchyma, although most gangliogliomas are relatively circumscribed tumors in imaging studies. Alterations in *BRAF* are recognized as the most frequent genetic alteration in gangliogliomas, particularly BRAF:p.V600E mutation, which has been reported in up to 50% of these tumors [10,15,43,46,53]. In the present series, 53% of gangliogliomas harbored *BRAF* alterations, both BRAF:p.V600E mutation and fusions. Other alterations were found in *NF1*, *NTRK2*, and *EWSR1*, but no other alteration was found at high frequency in these tumors.

A novel *SLMAP-NTRK2* gene fusion was identified by RNAseq in one parietal ganglioglioma (Supp. Fig. S11). This fusion employs a similar mechanism to the *NAV1-NTRK2* fusion previously reported by our group in an oligoastrocytoma [67], retaining the tyrosine kinase domain of NTRK2. *QKI-NTRK2* and *NACC2-NTRK2* fusions have previously been reported in pilocytic astrocytoma, in pediatric high-grade glioma and adult glioblastoma [25,63,23]. NTRK receptors modulate developmental signals within the nervous system, influencing induction of neurite outgrowth and neuronal differentiation, survival, and death. They activate the MAPK pathway following neurotrophin binding [36].

A novel *EWSR1-PATZ1* fusion was present in one ganglioglioma. A similar fusion involving these two genes has been described once before in an undifferentiated sarcoma that presented in the chest wall of a teenager [33]. PATZ1 is a BTB-ZF transcription factor that inhibits the ability of p53 to bind to its response elements and is involved in keeping embryonic stem cells in an undifferentiated state [28,37]. Rearrangement of *EWSR1* is found in intracranial Ewing sarcomas that involve the inner table of the skull and extraosseous meningeal 'peripheral' primitive neuroectodermal tumors [35,52]. Additionally, exceptional examples of other intracranial neoplasms with an *EWSR1* rearrangement and variable malignancy have been reported [13,18]. However, this is the first report of such a fusion gene in a primary neuroepithelial tumor.

Platelet-derived growth factor receptor α (*PDGFRA)* amplification and mutations have previously been reported in pediatric high-grade glioma and adult glioblastoma [40,9]. Dinucleotide *PDGFRA* somatic mutations were identified in 2 LGNTs; 1 DNET (LGNT42) and 1 oligoastrocytoma (LGNT92) (Supp. Fig. S12). Neither tumor was associated with an aggressive clinical course. LGNT42 had dinucleotide mutations on the same allele at chr4:55136831 and chr4:55136832 (AA>TT), while LGNT92 had dinucleotide mutations on the same allele at chr4:55136832 and cht4:55136833 (AG>TC). These changes introduced K385L and K385I mutations in LGNT42 and LGNT92, respectively. Notably, both mutations changed K385 from a basic amino acid to a hydrophobic amino acid. A dinucleotide *PDGFRA* mutation at K385 (AG>TA) introducing K385I has previously been reported in one pediatric high-grade glioma [54]. Additional *PDGFRA* K385M mutations have also been reported in one adult LGG and one adult HGG [67,54]. *BRAF:*p.V600E mutation was the most prevalent SNV (12/91) identified in the cohort, followed by SNVs in *FGFR1* (9/91) and *IDH1* (3/91). No additional recurrent SNVs or indels were identified in the study cohort. Genomic aberrations could not be determined for 6/91 (7%) cases; 3 gangliogliomas, 2 d-OTs and 1 DNET.

Recent genetic studies have helped to delineate pediatric-type and adult-type diffuse LGGs, which have very similar histopathological features. Adult-type disease demonstrates a high frequency of *IDH1/2* mutation [8,19,39,64], while recurrent genetic alterations in *MYB*, *BRAF*, or *FGFR1* have been found in small series of pediatric tumors [12,15,46,67]. Adult-type disease can present in adolescence as shown in the present data and other studies, and its distinction from pediatric-type disease is important, because anaplastic progression occurs in most adult-type grade II gliomas but rarely in histopathologically comparable pediatric-type tumors [26,60]. In this way, the molecular genetic characterization of LGGs

has important implications for how they are classified in the WHO classification of nervous system tumors [32].

Aside from supporting the important distinction between pediatric-type and adult-type diffuse LGGs, our findings have further diagnostic implications. Many CNS neuroepithelial tumors can contain OLCs or appear similar to diffuse astrocytomas, and in histopathologic preparations of small CNS biopsies distinguishing between such tumors can be difficult. Genetic analysis may aid diagnosis in this situation, by demonstrating one of the key alterations that would align a tumor to either the DNET/d-OT or AG/DA axis. Such analysis need not involve NGS; the key alterations described in our study can all be determined by conventional molecular pathology or cytogenetic methods on FFPE tissue preparations.

Additionally, targeted therapies are currently being tested for the key LGNT genetic alterations. Clinical trials investigating BRAF:p.V600E inhibitors are under way in pediatric patients, and a study of the mTOR inhibitor, Everolimus, in progressive pediatric LGG has recently been completed. Dovitinib (TKI258), an FGFR1/2/3 inhibitor, has shown anti-tumor activity in breast cancer patients with FGFR-amplified breast cancer [3]. On the basis of our findings, these developments would be predicted to benefit children and young adults with LGNTs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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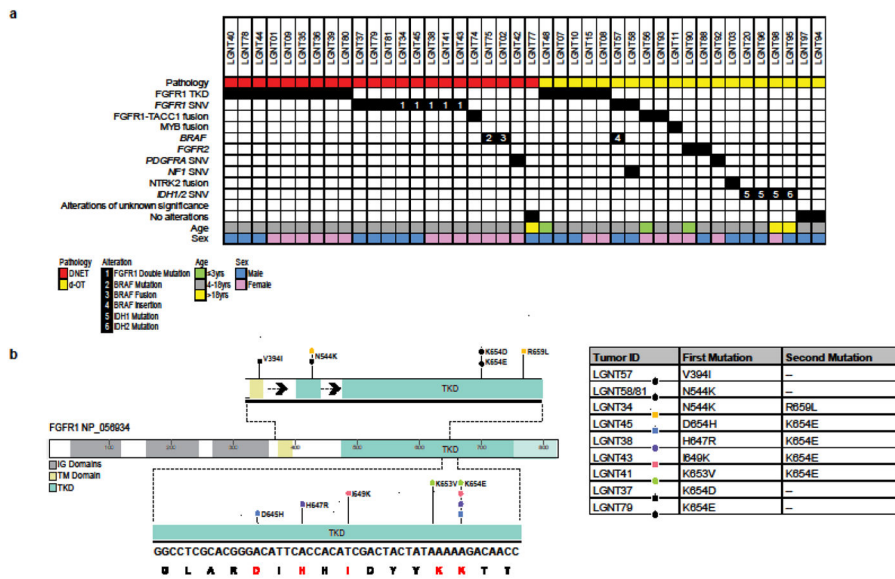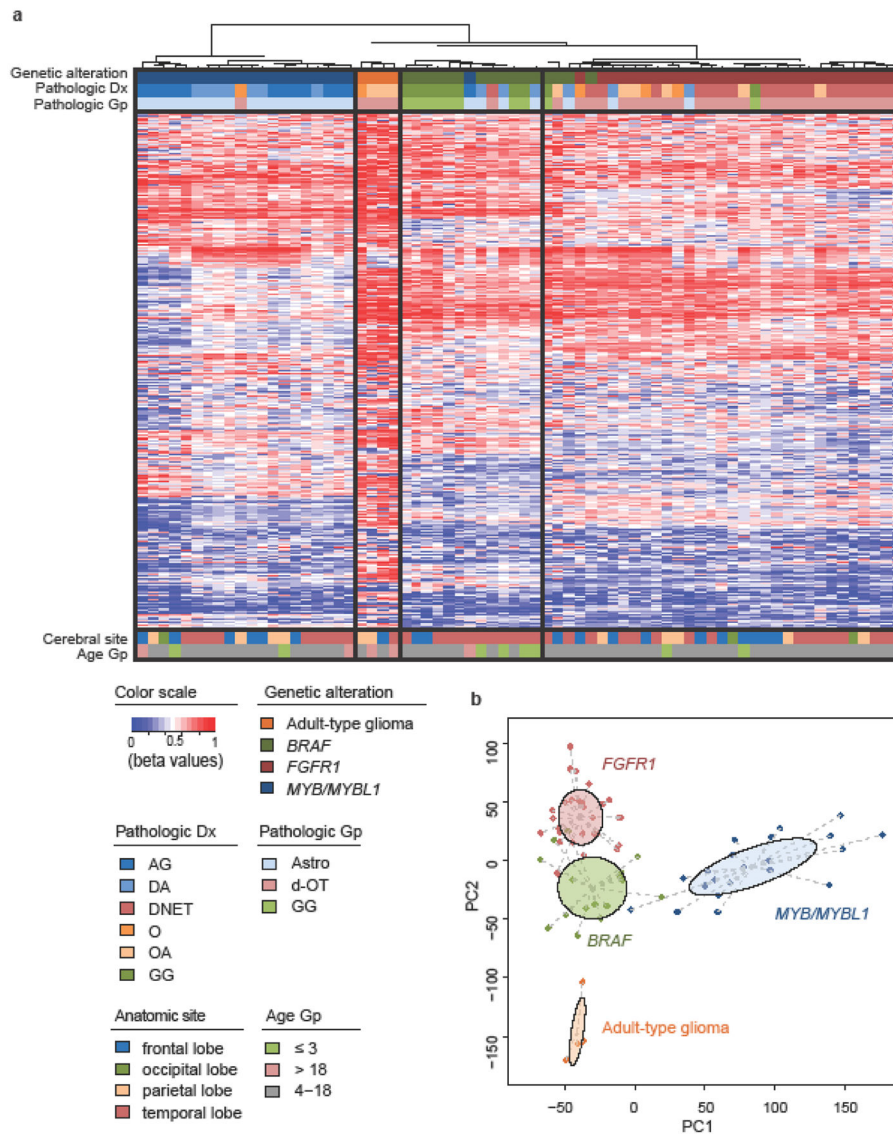
Figure 1.
Genetic alterations among 42 LGNTs with an oligodendroglial phenotype (a). *FGFR1* SNVs represented on the protein structure and tabulated, including four tumors with 'doublet' missense mutations on the same allele – lower part of diagram – and one tumor with two mutations, each on a different allele – upper part of diagram, with single mutations (b).
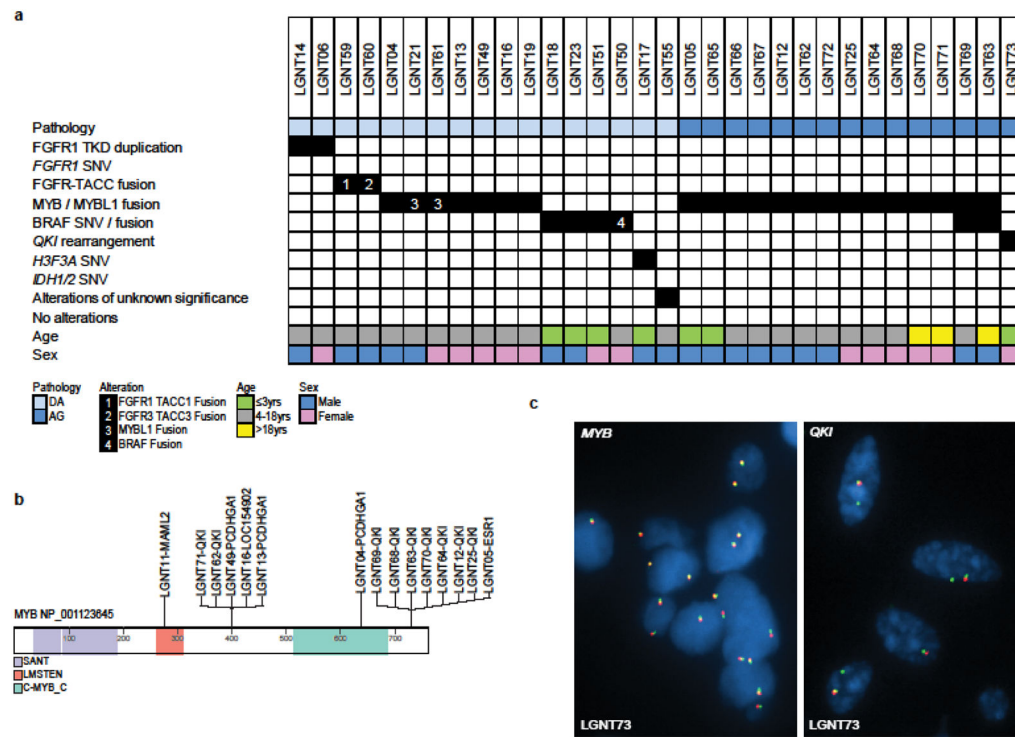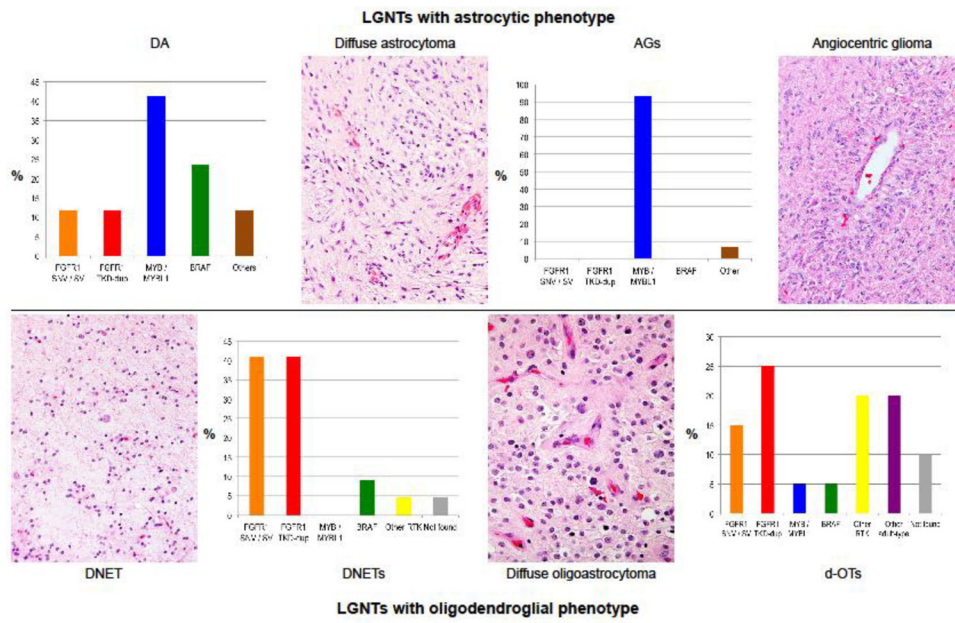
Figure 2.
Genetic alterations among 32 LGNTs with an astrocytic phenotype (a). Location of *MYB* fusion genes represented on protein structure (b). LGNT73 - iFISH profiles using *MYB* and *QKI* 'break-apart' probe sets and demonstrating rearrangement/deletion of *QKI*, but not *MYB*.
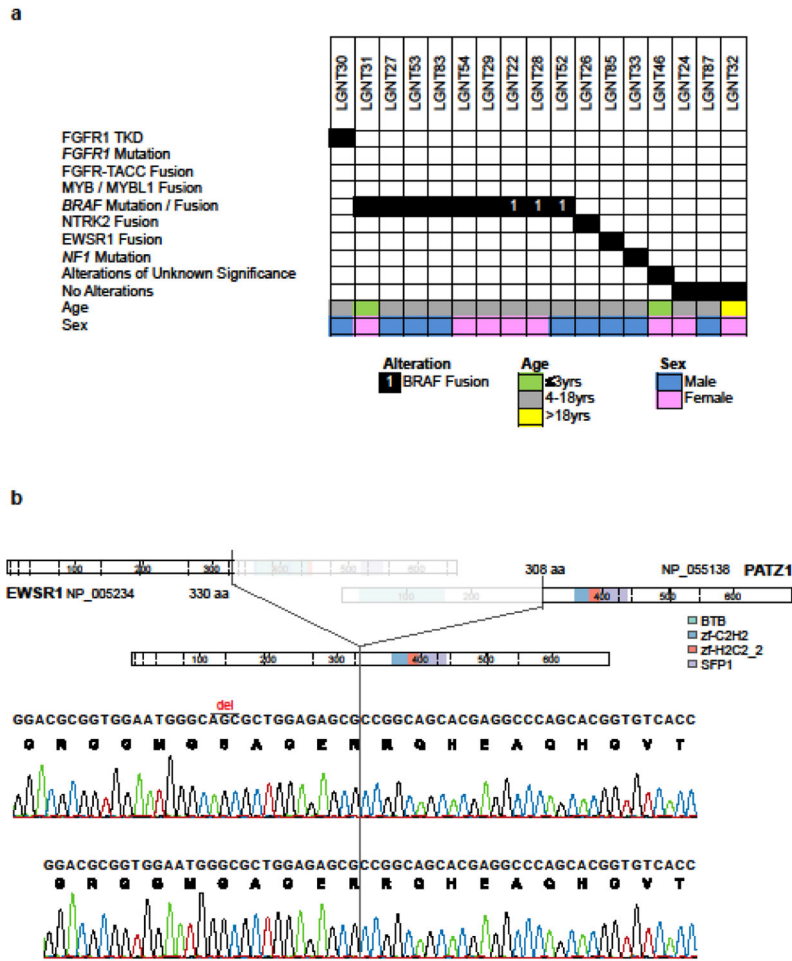
Figure 3.
Genetic alterations among 17 gangliogliomas (a). WGS, WES, or RNA-seq data were available for 15/17 tumors; LGNT83 and LGNT87 were analyzed by targeted approaches but not by NGS. Of nine gangliogliomas with *BRAF* alterations, six had a BRAF:p.V600E mutation. EWSR1-PATZ1 fusion (b). Two clones, differing only with respect to a 3-bp deletion ('del' over sequence trace), were independently validated. In the rearrangement, *PATZ1* loses its transcriptional repressor domain (BTB/POZ domain) at the N-terminus.

Figure 4.
DNA methylation-based data from LGNTs with *BRAF*, *FGFR1*, or *MYB/MYBL1* pathogenic alterations used in unsupervised hierarchical clustering (a), or principal components analysis (b). AG, angiocentric glioma; DA, diffuse astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; O, oligodendroglioma; OA, oligoastrocytoma; GG, ganglioglioma; Astro, astrocytic; d-OT, diffuse oligodendroglial tumor.

Figure 5.
Proportions of key genetic alterations in four types of LGNT divided into two axes according to histogenesis – astrocytic and oligodendroglial.

AG, angiocentric glioma; DA, diffuse astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; d-OTs, diffuse oligodendroglial tumors.

Table 1

Summary of published genetic alterations by histopathology

Study	Tumor	Number of cases	FGFR1 alteration (%)	MYB/MYBL1 alteration (%)	BRAF alteration (%)
Zhang et al., Nat Genet 2013 [67]	AG	2	0	100	0
	DA	23	17	26	26
	DNET	1	100	0	0
	d-OT	13	69	8	8
	GG	9	0	0	56
Roth et al., Cancer Genet, 2014 [51]	AG	1	nd	0	0
	DA	6	nd	0	17
	DNET	2	nd	0	50
	GG	2	nd	0	50
Ramkissoon et al., PNAS, 2013 [46]	AG	3	0	66	0
	DA	18	0	28	22
	GG	9	0	0	56
Prabowo et al., Brain Pathol, 2013 [43]	DNET	77	nd	nd	30
	GG	93	nd	nd	41
Chappé et al., Brain Pathol 2013 [10]	DNET	20	nd	nd	30
	GG	31	nd	nd	39
Cruz et al., J Neurooncol 2014 [12]	DA	17	nd	nd	29

AG, angiocentric glioma; DA, diffuse astrocytoma; DNET, dysembryoplastic neuroepithelial tumor; d-OT, diffuse oligodendroglial tumor; GG, ganglioglioma nd, not determined

References in brackets