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REVIEW

Recent Advances on the Molecular Pathology of Glial Neoplasms in Children and Adults

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Gliomas represent the most common primary intraparenchymal tumors of the central nervous system in adults and children and are a genetic and phenotypic heterogeneous group. Large multi-institutional studies and The Cancer Genome Atlas have provided firm insights into the basic genetic drivers in gliomas. The main molecular biomarkers routinely applied to evaluate diffuse gliomas include *MGMT* promoter methylation, *EGFR* alterations (eg, EGFRvIII), *IDH1* or *IDH2* mutations, and 1p19q co-deletion. Many of these markers have become standard of care for molecular testing and prerequisites for clinical trial enrollment. Other recent biomarkers include *TERT* promoter and *ATRX* mutations, alterations that identify specific molecular subgroups of diffuse gliomas with biological and clinical relevance. It has also become apparent that distinctive patterns of molecular genetic evolution develop in the context of current therapeutic regimens. Important insights have also been uncovered in the field of pediatric glioma, including the identification of recurrent mutation, fusion, and/or duplication events of the *BRAF*, *FGFR1*, *MYB*, and *MYBL1* genes in pediatric low-grade gliomas, mutations affecting histone components (*H3F3A* p.K27M or p.G34) in pediatric high-grade gliomas, and aggressive subsets developing in midline central nervous system structures. Here, we summarize current concepts in molecular testing for glial tumors, including recent findings by large-scale discovery efforts and technologic advances that are affecting routine diagnostic work. *(J Mol Diagn 2016, 18: 620–634; http://dx.doi.org/10.1016/j.jmoldx.2016.05.005)*

Molecular Pathology of Glial Neoplasms: General Concepts

Glial neoplasms encompass a heterogeneous group characterized predominantly by an astrocytic or oligodendroglial morphology. The group of diffusely infiltrating astrocytomas is the most frequent and includes diffuse astrocytoma (World Health Organization grade II), recognized by cytologic atypia and low-moderate cellularity; anaplastic astrocytoma (World Health Organization grade III), characterized by moderate-high cellularity and obvious mitotic activity; and, at the end of the spectrum, glioblastoma (World Health Organization grade IV), containing necrosis or microvascular proliferation. Glioblastoma is also a morphologically heterogeneous neoplasm, with several

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variants and patterns.[1] For example, the small cell astrocytoma pattern demonstrates minimal pleomorphism, but it tends to affect older age groups, has an aggressive course and frequent epidermal growth factor receptor (*EGFR*) (amplification in 70%), and phosphatase and tensin homolog (*PTEN*)/10q (approximately 100%) alterations. Conversely, giant cell glioblastoma is characterized by voluminous cell size and frequent *TP53* mutations (83%) and aurora kinase B (*AURKB*) overexpression. Epithelioid glioblastoma may resemble a variety of non-central nervous system (CNS) tumor types, and of relevance has B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) p.V600E mutations in approximately 50% of the cases. Gliosarcoma is characterized by neoplastic glial and mesenchymal components and a molecular profile similar to conventional glioblastoma but a lower frequency of *EGFR* amplification (<8%). Glioblastoma may be further subdivided on a clinical basis into primary and secondary subtypes, the latter evolving from documented or putative lower grade astrocytoma precursors and sharing with them early genetic driver events, for example, $NADP^+$-dependent isocitrate dehydrogenase 1 or 2 (*IDH1* or *IDH2*) gene mutations.[2]

Oligodendroglial tumors include low-grade oligodendroglioma (World Health Organization grade II) and anaplastic oligodendroglioma (World Health Organization grade III). The hallmark of oligodendroglial tumors is the presence of cellular monotony, including round nuclei with fine chromatin and a small nucleolus. Brisk mitotic activity, endothelial hypertrophy, and necrosis characterize the anaplastic oligodendrogliomas. The category of mixed glioma or oligoastrocytoma has increasingly fallen out of favor, given its low reproducibility and the lack of a distinguishing molecular signature from either astrocytic or oligodendroglial neoplasms in almost all instances.[3]

The circumscribed glioma group has a predilection for children and young adults and includes pilocytic astrocytoma (World Health Organization grade I), subependymal giant cell astrocytoma (World Health Organization grade I), and pleomorphic xanthoastrocytoma (World Health Organization grade II). At the molecular level, these neoplasms have frequent alterations in components of the mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) signaling pathways, often as the single genetic driver.

Although classic histology-based grading schemes have proven valuable in neuro-oncology practice for decades, it has been increasingly recognized that molecular genetics-based classification schemes provide robust prognostic information. The identification of key driver mutations in glial tumors, including activating mutations in oncogenes and inactivation of tumor suppressor genes, has been increasingly facilitated by the greater availability of high-throughput molecular assays and the development of immunohistochemical tests that more specifically identify key alterations in a practical manner.[4] Updated diagnostic categories have

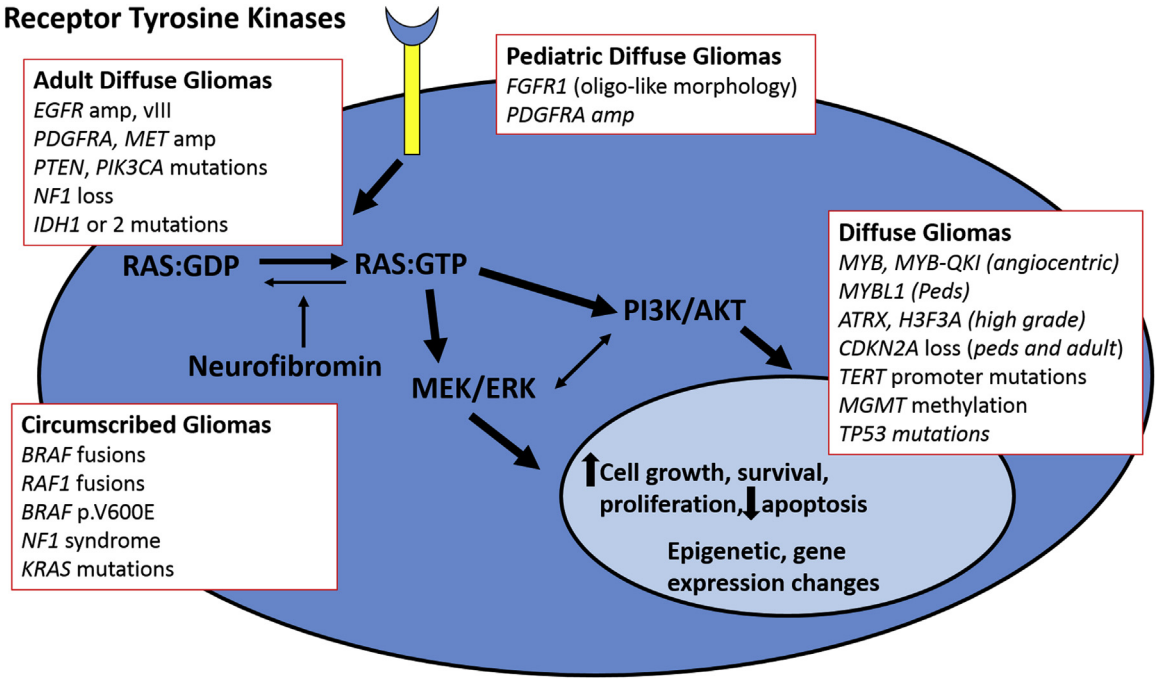

Figure 1 Signaling pathways relevant to glial neoplasms in adults and children. A variety of signaling pathways are activated through mutations of oncogenes or tumor suppressor genes in diffuse gliomas in adults and children. MAPK pathway activation through receptor tyrosine kinase activation or downstream gene mutations and rearrangements (*BRAF*, *NF1*, *RAS*) is a universal feature of glial neoplasms. The PI3K/mTOR pathway is also activated through receptor tyrosine kinase activation and downstream gene mutations (*PTEN*, *PI3KCA*). Other relevant alterations include mutations affecting metabolic and epigenetic pathways (*IDH1*, *IDH2*, *H3F3A*) and telomere activity and/or maintenance (*TERT*, *ATRX*). Although there is some overlap regarding the pathways activated in adult and pediatric gliomas, the specific alterations and/or frequencies differ in these two broad subgroups. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase.