Oncology Learning Network

Genetic Mechanisms of Pediatric Low-Grade Glioma: Oncogenic Drivers and the Molecular Landscape

Pediatric low-grade glioma (pLGG) is the most common central nervous system tumor in childhood.[1,2]

Nearly 70% of pLGG cases harbor genomic driver mutations in the mitogen-activated protein kinase (MAPK) signaling pathway.[3]

Continuous activation of the MAPK signaling pathway can result from[4]:

- Activating mutations
- In-frame fusions of signaling components
- Loss of function mutations in negative regulators

Continuous activation of MAPK signaling can lead to the uncontrolled cell proliferation and survival observed in pLGG.[4]

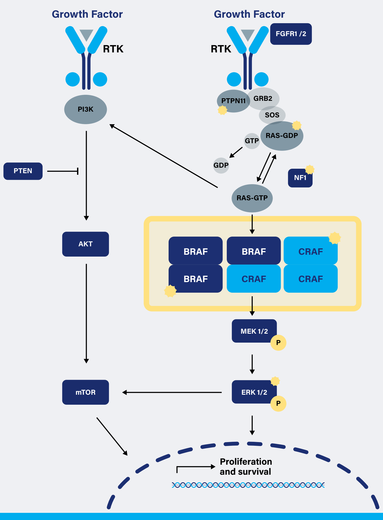
The Role of *BRAF* Mutations

Structural variants in the *BRAF* gene are the most common oncogenic driver, found in approximately 70% of all sporadic pLGG.[1]

BRAF alterations lead to continuous MAPK signaling pathway activation, which promotes cell proliferation, survival, and dedifferentiation.[4]

Activating *BRAF* mutations can occur as point mutations, in-frame deletions, or fusions with other kinases.[4]

MAPK Signaling in pLGG[4]



Clinical Relevance

Surgical resection remains the mainstay of front-line therapy for symptomatic pLGG.[3]

However, more than 50% of pLGGs occur in locations that are either not amenable to surgery or are only amenable for limited dissection.[3]

Several targeted therapies have been developed to manage.[3]

- *BRAF* inhibitors specifically target *BRAF* mutations
- MEK inhibitors target the MAPK pathway

References

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2. O'Hare P, Cooney T, de Blank P, et al. Resistance, rebound, and recurrence regrowth patterns in pediatric low-grade glioma treated by MAPK inhibition: a modified Delphi approach to build international consensus-based definitions-International Pediatric Low-Grade Glioma Coalition. *Neuro Oncol*. 2024;26(8):1357-1366. doi: 10.1093/neuonc/noae074.
3. Crotty EE, Sato AA, Abdelbaki MS. Integrating MAPK pathway inhibition into standard-of-care therapy for pediatric low-grade glioma. *Front Oncol*. 2025;15:1520316. doi: 10.3389/fonc.2025.1520316.
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