Disseminated pediatric low-grade glioma study

Findings of: Levine AB, Bennett J, Patil P, Burns I, Siddaway R, Li C, Haizel-Cobbina J, Rana M, Yuditskiy R, Son A, Nakano Y, Patel P, Ho IC, Ku M, Lyons AT, Velázquez Vega JE, Schniederjan MJ, Erker C, Cacciotti C, Santi M, Nelson EJ, Cheng S, Dunham C, Wilson B, Black K, Van Landeghem F, Nobre L, Eisenstat DD, Stücklin ASG, Weiser A, Larouche V, Giannakouros P, Fonseca A, Williamson L, Fernandes IL, Plant-Fox AS, Fleming A, Campbell S, Mushtaq N, Bukhari SI, Minhas K, Graham RT, Raskin S, Jadrijevic-Cvrlje F, Ludlow L, Macneil MV, Mulcahy-Levy JM, Demarsh S, Fukuoka K, Yamasaki K, Suzuki T, Ohka F, Kawamura A, Arakawa Y, Ishihara T, Yamasaki F, Hansford JR, Luck A, Nasrallah MP, Toledano H, Masoud RM, Lassaletta A, Blasco-Santana L, Kilday JP, Talianski A, Davies C, Johnston J, Hale AT, Dirks PB, Rutka JT, Dewan MC, Tabori U, Hawkins CE. Integrated clinical and molecular landscape of disseminated pediatric low-grade glioma. Neuro Oncol. 2025 Oct 21:noaf245. doi: 10.1093/neuonc/noaf245. Epub ahead of print. PMID: 41117845.

Here is a detailed summary and commentary on the findings from **Levine et al. "Integrated clinical and molecular landscape of disseminated pediatric low-grade glioma" (Neuro-Oncol, 2025, noaf245)** OUP Academic +2 PMC +2

Context & Rationale

- **Pediatric-type low-grade gliomas (PLGGs)** are common CNS tumors in children, and most follow an indolent course. However, a small fraction exhibits **dissemination** (spread within the central nervous system), which is rare but associated with worse outcomes. PMC +2 OUP Academic +2
- Because dissemination in PLGG is poorly understood and challenging to treat, Levine et al. assembled the largest international cohort to date (n = 269) of **disseminated PLGG** cases with integrated clinical and molecular data, including DNA sequencing and methylome (DNA methylation) profiling. OUP Academic +2 PMC +2
- Their aims were: (1) to define clinical subtypes of dissemination, (2) to delineate molecular features (mutations, methylation patterns) associated with dissemination, and (3) to assess therapeutic outcomes, particularly in relation to targeted therapy vs conventional chemotherapy. PMC +1

Key Findings

Clinical Subtypes and Prognosis

- The authors identified **three subgroups** of disseminated PLGG based on the **timing** and **spatial pattern** of dissemination:
  1. **De novo leptomeningeal dissemination without a visible primary mass**
  2. **Dissemination occurring at the time of primary diagnosis (synchronous dissemination)**
  3. **Dissemination occurring later (metachronous) from an established primary tumor** PMC +2 OUP Academic +2

- Among these, **infants** and those with **diffuse leptomeningeal-only disease** (i.e. spread in CSF/meninges without a solid mass) had the **poorest clinical outcomes**. PMC +2 OUP Academic +2

- Interestingly, other dissemination patterns (e.g. metachronous spread from a known primary) had relatively more favorable survival, although still worse than non-disseminated PLGG in general. PMC +2 OUP Academic +2

Molecular Landscape: Overlap with Non-disseminated PLGG

- One central finding is that **genetic alterations in disseminated PLGG substantially overlap** with those observed in **non-disseminated PLGG** (i.e. the "typical" indolent cases). PMC +2 OUP Academic +2

- This implies that **dissemination is not generally driven by unique recurrent mutations** but likely involves **non-genetic mechanisms**, such as epigenetic, microenvironmental, developmental or cellular state factors. PMC +1

- The methylation profiling did yield substructure and allowed classification, but no clear "dissemination-specific" methylation signature was robustly associated beyond what is known for PLGG broadly. OUP Academic +1

- The study suggests that **non-genetic processes** (e.g. cellular plasticity, microenvironmental cues, CSF dynamics, epigenetic regulation) may be critical in enabling or promoting the ability of tumor cells to disseminate. PMC +1

Therapeutic Implications & Outcomes

- In this retrospective cohort, **targeted therapy** against the **RAS/MAPK pathway** (which is a key driver pathway in many PLGGs) **outperformed conventional chemotherapy**, whether used as first-line or second-line therapy, in terms of disease control in disseminated disease. PMC +2 OUP Academic +2

- This supports the notion that **targeted inhibition of MAPK signaling** should be strongly considered (or prioritized) in disseminated PLGG settings, even in the first- or second-line context. OUP Academic +1
- The authors caution, however, that due to the retrospective and heterogeneous nature of the data (e.g. variable prior therapies, non-uniform protocols), these therapeutic observations are **hypothesis-generating** rather than definitive evidence. PMC +1

Interpretation, Strengths & Limitations

Strengths:

- This is the **largest and most comprehensive series** of disseminated pediatric low-grade glioma to date, with international collaboration, and integration of both clinical and molecular data. OUP Academic +2 PMC +2
- Use of **methylome profiling** in addition to DNA sequencing helps to contextualize epigenetic/epigenomic landscape in disseminated tumors. OUP Academic +1
- The stratification by dissemination timing/spatial patterns provides a more nuanced clinical classification, which may inform prognosis and trial design.

Limitations:

- Retrospective in nature, with non-uniform treatment regimens, variable imaging protocols, and selection biases.
- Central pathology review may not have been fully uniform across all centers, potentially causing heterogeneity in tumor classification.
- Therapeutic comparisons (targeted therapy vs chemotherapy) are not from randomized trials, so confounding (patient selection, prior therapies, performance status) may influence outcomes.
- Although methylation and mutation overlap with non-disseminated PLGG is shown, mechanistic drivers of dissemination remain speculative and require functional validation.

Significance & Future Directions

- The finding that **dissemination is not typically associated with unique recurring mutations** suggests that future research should focus on **non-genetic drivers** (e.g. epigenetic reprogramming, tumor-microenvironment interactions, cell state transitions, CSF niche biology).
- The clinical classification proposed could be used to **design stratified trials**, e.g. separating infants, leptomeningeal-only disease, and metachronous dissemination.

- The favorable signal for **MAPK-targeted therapy** in this context strengthens the rationale for **prospective trials** of such agents in disseminated PLGG, possibly even earlier in the disease course.
- Further work could include **longitudinal sequencing / liquid biopsy / single-cell profiling** of CSF / disseminated lesions to track dissemination evolution, and to identify biological vulnerabilities unique to the disseminative phenotype.

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