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No safe harbors for recurrent posterior fossa group A ependymoma: A time for change in risk assignment?

Jordan R. Hansford and David D. Eisenstat

Michael Rice Cancer Centre, Women's and Children's Hospital, North Adelaide, South Australia, Australia (J.R.H.); Precision Cancer Medicine, South Australia Health and Medical Research Institute, Adelaide, South Australia, Australia (J.R.H.); South Australia Immunogenomics Cancer Institute, University of Adelaide, Adelaide, South Australia, Australia (J.R.H.); Children's Cancer Centre, Royal Children's Hospital, Parkville, Victoria, Australia (D.D.E.); Stem Cell Biology, Murdoch Children's Research Institute, Parkville, Victoria, Australia (D.D.E.); Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia (D.D.E.)

Corresponding Author: Jordan R. Hansford, BScH, MSc, MBBS, FRACP, Michael Rice Cancer Centre, Women's and Children's Hospital, North Adelaide, SA 5006, Australia (jordan.hansford@sa.gov.au); David D. Eisenstat, MD, MA, FRCPC, FRACP, Children's Cancer Centre, The Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville VIC 3052 Australia (david.eisenstat@rch.org.au).

In this issue, Donson et al. report on the results of a longitudinal, multicenter retrospective study of posterior fossa group A ependymomas (PFA EPNs). Using DNA methylation, bulk RNAseq, single nuclei RNAseq and immunohistochemistry (IHC), the authors charted clinical, genomic, and cellular trajectories between the tumors at presentation and at recurrence. This study furthers the evidence for both 1q gain (1q+) and 6q loss (6q–) copy number variations (CNV) characteristic of ultra-high-risk (UHR) ependymoma.[1] In fact, these factors increase over time in paired primary and relapsed tissues from 23% at presentation to 61% of all samples at first recurrence.[1] Although previous studies[2–4] have demonstrated poor outcomes for all patients with these CNV, what was unclear was the timing of the acquisition or loss of these critical chromosome arms, respectively. This multicentre study convincingly shows the evolution and increased prevalence of these changes in relapsed PFA ependymoma.

Underlying these changes are heterochromatin-associated "Open Sea" CpG hypomethylation runs that correlate with and may predispose the patient to CNV (Figure 1). The open chromatin structure and repeat DNA segments have previously been associated with DNA instability and chromosomal events consistent with this study.[5–7] Clinically, with the combination of adverse copy number changes and the open sea conformation, all patients harboring these aberrations should be risk-stratified as high, if not UHR as suggested previously.[4] Future studies must incorporate these risk features early in the patient's journey rather than at relapse to better optimize patient outcomes with new and novel therapies. However, patients without 1q+/6q– have markedly better clinical outcomes, and conventional therapies may be more appropriate for this clinical cohort at diagnosis.

Previous studies have shown the epigenetic nature of PFA ependymoma. Mack et al. reported that PFA ependymoma is epigenetically silenced through CpG island hypermethylation leading to convergence on the polycomb repressive complex (PRC2) and repression of differentiated genes through trimethylation of H3K27.[7] This subsequently led to the development and testing of the immunohistochemical loss of detection of H3K27 trimethylation (H3K27me^3) as predictive of PFA subgrouping.[8] In a subset of patients from the current study, 11 of the 12 patients retained loss of H3K27me^3 at first recurrence. In clinical practice, the H3K27me^3 marker is also used in combination with H3K27M IHC to identify diffuse midline glioma (DMG). Of significance, in DMG, a treatment-resistant and invariably fatal disease, ~20% are without canonical H3.3/3.1K27M mutations but also demonstrate H3K27me^3 loss. Several groups have also shown rare, but occasional H3K27M mutations in ependymoma.[9,10] Furthermore, adverse CNV in PFA are also implicated in worse DMG outcomes with 1q+ associated with poor outcome in H3.1K27M (but not H3.3K27M) and 6q– trending to worse outcomes. Together, the combination of these findings supports convergent underlying biological mechanisms resulting in similar poor outcomes of both PFA and DMG with their inherent treatment resistance.[11]

Given the global methylation changes in ependymoma, investigators have attempted to modulate the epigenome to improve clinical outcomes (NCT03206021). Using DNA methyltransferase inhibition (azacitadine) in combination with chemotherapy, it was hypothesized that the relative lack of chemosensitivity of these tumors could be overcome. However, with areas of hypermethylated CpG islands and contrasting hypomethylated regions at risk of future CNV events in PFA, we eagerly await the release of the findings of this study and the future implications of developing epigenetic therapy for this disease.

The authors also used spatial transcriptomics in a subset of paired patient samples to show a unique, highly

Figure 1. The left panel represents an ultra-high-risk PFA ependymoma with 1q+/6q– copy number variations experiencing a challenge sailing in the open (chromatin) sea, whereas the right panel represents a more standard risk PFA without 1q+/6q– in still waters in the safety of the harbor.

treatment-resistant, undifferentiated neuroepithelial progenitor-like cell (UEC-A) group that is selected for the high-risk patients at relapse. Furthermore, IHC scoring of COL9A2 (collagen type IX alpha 2) appeared promising as a marker of this UEC-A cell population that warrants further study. Co-localized with this group are non-neoplastic myeloid lineage immune cells that may offer a unique immunotherapy target for these UHR patients. To date, immunotherapy in PFA ependymoma has not been successful.[12] However, new agents targeting other immune mediators may be more efficacious as more knowledge is gained about unique tumor microenvironment interactions in these UHR patients, including, for example, anti-CD47 agents to assist in myeloid immune activation.

The authors suggest the adoption and incorporation of methylation profiling into future clinical trials and tumor classification in the pathology department. While we fully agree with the authors, unfortunately, this testing remains beyond the reach of most international sites apart from academic centers in North America, Europe, and Australia. Importantly, validation of open-seas hypomethylation patterns in prospective studies via methylome analysis needs to be undertaken. For those where methylation analysis is not yet available, analysis of aneuploidy should be encouraged using other traditionally reliable methods and continue to be applied to novel clinical trials focused on this UHR PFA group.

As we continue to unwind the intricate epigenomic controls of this disease, we will hopefully grow closer to finding new and novel agents this UHR patient group desperately needs to arrive at safer harbors.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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