Neuro-Oncology Advances

6(1), vdae208, 2024 | https://doi.org/10.1093/noajnl/vdae208 | Advance Access date 7 December 2024

A scoping review of diffuse hemispheric glioma, H3 G34-mutant: Epigenetic and molecular profiles, clinicopathology, and treatment avenues

Kayen Tang, Melissa Cesaire, Taylor McDonald, Patrick J. Cimino, Maria G. Castro, and Sadhana Jackson

All author affiliations are listed at the end of the article

Corresponding Author: Sadhana Jackson, MD, Developmental Therapeutics and Pharmacology Unit, Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke (NINDS), NIH, Building 10, Room 7D45, 10 Center Drive, Bethesda, MD 20892, USA (Sadhana.jackson@nih.gov).

Abstract

Background. Survival of pediatric and young adults with malignant glioma remains poor despite progress in treatment. This is especially true for diffuse hemispheric glioma (DHG), H3 G34-mutant, which is often present in adolescent and young adult patients. This scoping review consolidates existing knowledge of DHG H3 G34-mutant and identifies future targets and therapeutic options. By streamlining this information, we aim to elucidate knowledge gaps in the field to better inform the community and motivate future research efforts.

Methods. In October 2024, MEDLINE, Embase, Cochrane Library, and Web of Science Core Collection were searched. Two reviewers screened all articles by title and abstract review and 3 independent reviewers extracted all studies meeting inclusion criteria relevant to H3G34R/V tumors (preclinical and clinical studies).

Results. Of the 2203 articles screened, 220 were deemed eligible (79 literature reviews, 7 systematic reviews, 63 preclinical studies, and 71 clinically oriented studies). We found that the United States and *Acta Neuropathologica* were the top country and journal contributors, respectively.

Conclusion. For this disease, it is critical to the field to conduct further research related to complexities of the tumor microenvironment, translation of preclinical studies to therapeutic early phase trials, and determining the role of targeted central nervous system drug delivery, so as to improve disease prognosis and survival.

Key Points

- Diffuse hemispheric glioma, H3 G34-mutant confers poor prognosis in adolescent/young adults.
- Scoping review outlines H3G34R/V glioma studies to date.
- Future research is warranted on the tumor microenvironment, opening Phase 1 trials, and targeted CNS drug delivery.

In the United States, cancer is one of the leading causes of child and adolescent death.[1] Despite advances in many types of pediatric and young adult cancers, treatment for brain cancer has proven exceedingly difficult, specifically for high-grade gliomas (HGGs), which have a 5-year survival rate of <15%.[2] Previous research has implicated histone H3-3A (Histone 3.3 or H3.3) as an important oncogenic regulator.[3–8] H3F3A is known to have 2 mutations linked to aggressive glioma phenotype: H3 p.K28M (K27M) and H3.3 p.3G35R/V (G34R/V). The H3K27M mutation occurs from a mutation of lysine to methionine at codon 28 and gliomas with this mutation are classified as diffuse midline glioma (DMG), H3 K27M-altered by the World Health Organization (WHO) and have a 99% 5-year mortality rate.[7,9,10] Conversely, H3.3G34R/V occurs from a mutation of a glycine residue to arginine (G34R) or valine (G34V) at codon 35. High-grade gliomas harboring H3.3G34R/V were previously classified with IDH-wildtype glioblastomas but have now been recognized as the distinct tumor type, diffuse

Published by Oxford University Press on behalf of the Society for Neuro-Oncology and the European Association of Neuro-Oncology 2024. This work is written by (a) US Government employee(s) and is in the public domain in the US.

hemispheric glioma (DHG), H3 G34-mutant, and WHO grade 4.[10–12] The overall survival of DHG H3.3G34-mutant is debated, but the consensus is that it has a dismal prognosis with a slightly improved median survival when compared with that of DMG H3 K27-altered.[13–15] H3 G34-mutant and H3 K27-altered gliomas each present a distinct genetic landscape that is being actively investigated.[16–18]

Despite a growing body of research on the clinicopathologic and genetic landscape of pediatric-type diffuse HGGs, there remains limited available information on the pathogenesis and optimal treatments for DHG H3 G34-mutant; beyond up-front surgical resection and chemoradiation. One reason this may be due to the reported incidence of DHG H3 G34-mutant is half that of the already rare DMG H3K27-altered.[10–12] There has been a steep increase in the number of studies conducted recently regarding DHG H3 G34-mutant. These investigations include case reports, preclinical studies, cohort studies, and literature reviews. However, there seems to be little information that objectively examines the current landscape of our understanding of H3.3G34R/V gliomas and outlines future therapeutic avenues yet to be explored. In this scoping review, we methodically evaluated current literature to summarize disease understandings along with successes and failures of treatments to date; all with the intention to improve therapeutics and survival. The objective of our scoping review is centered on consolidating current understandings of the disease, outlining critical gaps in knowledge, and detailing unexplored areas for future research that may contribute to a better overall understanding of DHG H3 G34-mutant.

Methods

This review was guided by the methodological framework developed by Arksey and O'Malley and further refined by Levac et al. and updated by Joanna Briggs Institute (JBI) methodology for scoping reviews.[19–21] We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Supplementary Material 1). The inclusion criteria spanned various designs (experimental, observational, clinical, and reviews) that extensively discussed DHG H3 G34-mutant within the central nervous system (CNS). Studies of all age groups and years of publication were also included. Exclusion criteria included the following: no available English text, full text not accessible, different publication type (commentaries, editorials, book, book chapters, lectures, preprints, errata, and conference proceedings/abstracts), no discussion of DHG H3 G34-mutant, and duplication: interim results updated in a more recent publication.

Database searches were conducted by a biomedical librarian (GB) in October 2023, from the available date of inception and updated in October 2024. The following databases were searched: MEDLINE via PubMed (National Library of Medicine), Embase (Elsevier), Cochrane Library (Wiley & Sons), and Web of Science Core Collection (Clarivate Analytics). In addition to database searches, we performed forward and backward citation searches which included relevant articles (Supplementary Material 2) An initial pilot was performed with Covidence (Veritas Health Innovation, available at www.covidence.org) screening software by 2 reviewers (K.T. and M.C.) using a sample of records to test and help refine the eligibility criteria and data extraction form. These measures assisted in ensuring inclusion/exclusion criteria were being applied consistently by reviewers. Following the pilot, the completed full search was performed, and all database records were imported into EndNote 20 (Clarivate) reference manager where duplicates were removed, and records were then imported into Covidence.

Using Covidence software, 3 reviewers (K.T., M.C., and T.M.) independently conducted title, abstract, and full-text screening for eligibility based on the inclusion and exclusion criteria previously detailed. Screening conflicts were resolved by discussion between 2 reviewers and the principal investigator. Three reviewers (K.T., M.C., and T.M.) extracted the following data from each study: title, journal, country of study, aim of study, main takeaways, study design, publication date, clinical/diagnostic information, disease classification (molecular and/or histologic), comparison to DMG H3 K27-altered tumors, emerging techniques, challenges to treatment, future treatment options, and clinical population descriptions if relevant. Data were then charted by reviewers (K.T., M.C., and T.M.) into Microsoft Excel for further analyses.

Results

Literature Search and Characteristics of Studies

A total of 4863 records were retrieved from the database searches. From these records, 2446 articles remained after the removal of 2417 duplicate records. Out of the 2446 articles screened for title and abstract, 2106 studies were deemed irrelevant, and 340 articles were assessed for full text eligibility. A total of 220 articles were included in our final analysis. The majority of excluded full-text articles had the incorrect study emphasis ($n = 103$), wrong study design ($n = 16$), or wrong patient population ($n = 1$) (Figure 1).

The 220 articles that met the inclusion criteria were identified as 79 literature reviews, 7 systematic reviews, 63 preclinical studies (47 focused on in vitro work, 5 focused on in vivo studies, and 11 included a combination of both), and 71 clinically oriented studies. We found that the top 5 producing countries of published papers were the United States, United Kingdom, Germany, China, and Canada, respectively (Table 1). Furthermore, the top 5 represented journals were *Acta Neuropathologica*, *Acta Neuropathologica Communications*, *Neuro-Oncology*, *Journal of Neuro-Oncology*, and *Cancer Cell*, in that respective order. We also identified a general increase in the number of papers published on DHG H3 G34-mutant in the last 7 years. Supplementary Table 1 specifically details the 220 studies with delineations of clinical, in vitro, combined preclinical/clinical and in vitro, and systemic reviews. In total, these studies provide a comprehensive finding of the impact of genetic events on disease prognosis, data relevant to drug delivery, and molecular

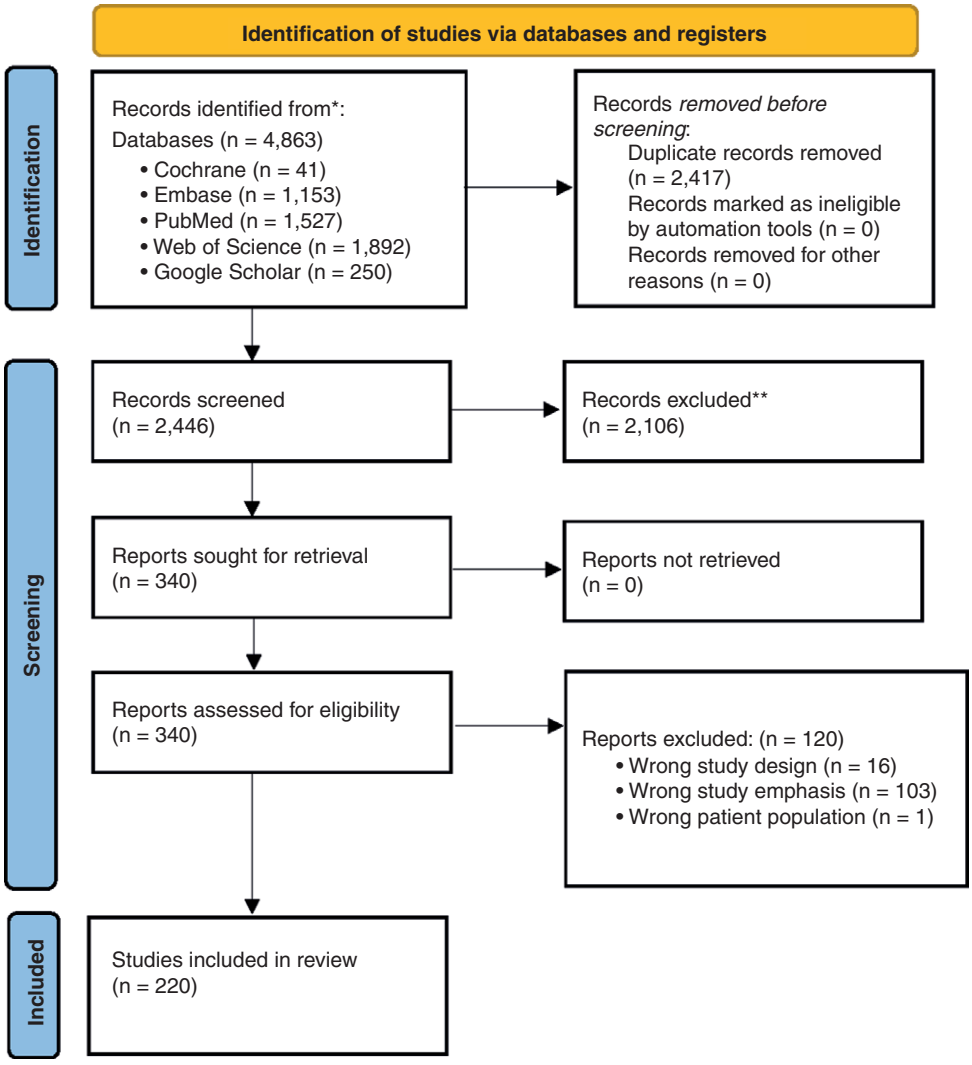

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart diagram. This PRISMA flow chart details an overview of the study inclusion and selection process. We screened 2446 studies, among which we deemed 220 as eligible and subsequently reviewed based on comprehensive selection criteria. Refer to Supplementary Material 2 for further details on included and excluded studies and reasons for exclusion as well as the results of consensus quality appraisal.

classifications, all in comparison to emerging diagnostic techniques and therapeutic targeting.

Histopathology of DHG G34-Mutant

Given the recent growing clinicopathologic knowledge of this tumor, DHG G34-mutant was added as a new tumor type in the 2021 fifth edition of the WHO Classification of Tumors of the CNS. These tumors are generally diffusely infiltrating astrocytic gliomas with elevated mitotic activity and glioblastoma-like features, including palisading necrosis and/or microvascular proliferation (Figure 2A–D). In some cases, the neoplastic cells have a giant cell morphology, including multinucleation (Figure 2E). In addition to, or sometimes alternatively to, a diffuse glioma component, the tumor can appear as an embryonal component (Figure 2F). In some cases, this embryonal component may compose most or all of the tumor, and older literature had placed these tumors into the waste basket term of CNS primitive neuroectodermal tumors (PNETs).[22] The immunohistochemical phenotype of DHG G34-mutant shows variable expression for glial fibrillary acidic protein (GFAP), which may be absent in embryonal component areas. Likely, due to the GABAergic interneuronal lineage of G34-mutant, SOX10 nor OLIG2 (oligodendrocyte maturation markers) transcription factors are not likely to have high expression.[17,23–25] DHG G34-mutant also frequently has overexpression of p53 along with nuclear loss of α-thalassemia/mental retardation syndrome-X-linked (ATRX). Mutation-specific antibodies for H3 G34R and G34V can be used to demonstrate these mutations; however, they are neither specific nor sensitive (discrepancy

Table 1. Studies Produced by Country, Journal, and Year or Publication. Top 5 Producers of Relevant Published Papers by Country, Journal, and Year of Publication. The Numerical Value Inside the Parenthesis Indicates the Number of Published Papers in the Respective Category

		Factors		
		Countries	Journal	Publish year
Ranking and number of published papers	First	United States (89)	*Acta Neuropathologica* (24)	2023 (31)
	Second	United Kingdom (23)	*Acta Neuropathologica Communications* (13)	2021 (30)
	Third	China (19)	*Neuro-Oncology* (23)	2022 (27)
	Fourth	Germany (17)	*Journal of Neuro-oncology* (9)	2020 (26)
	Fifth	Canada (15)	*Cancer Cell* (9)	2024 (18)

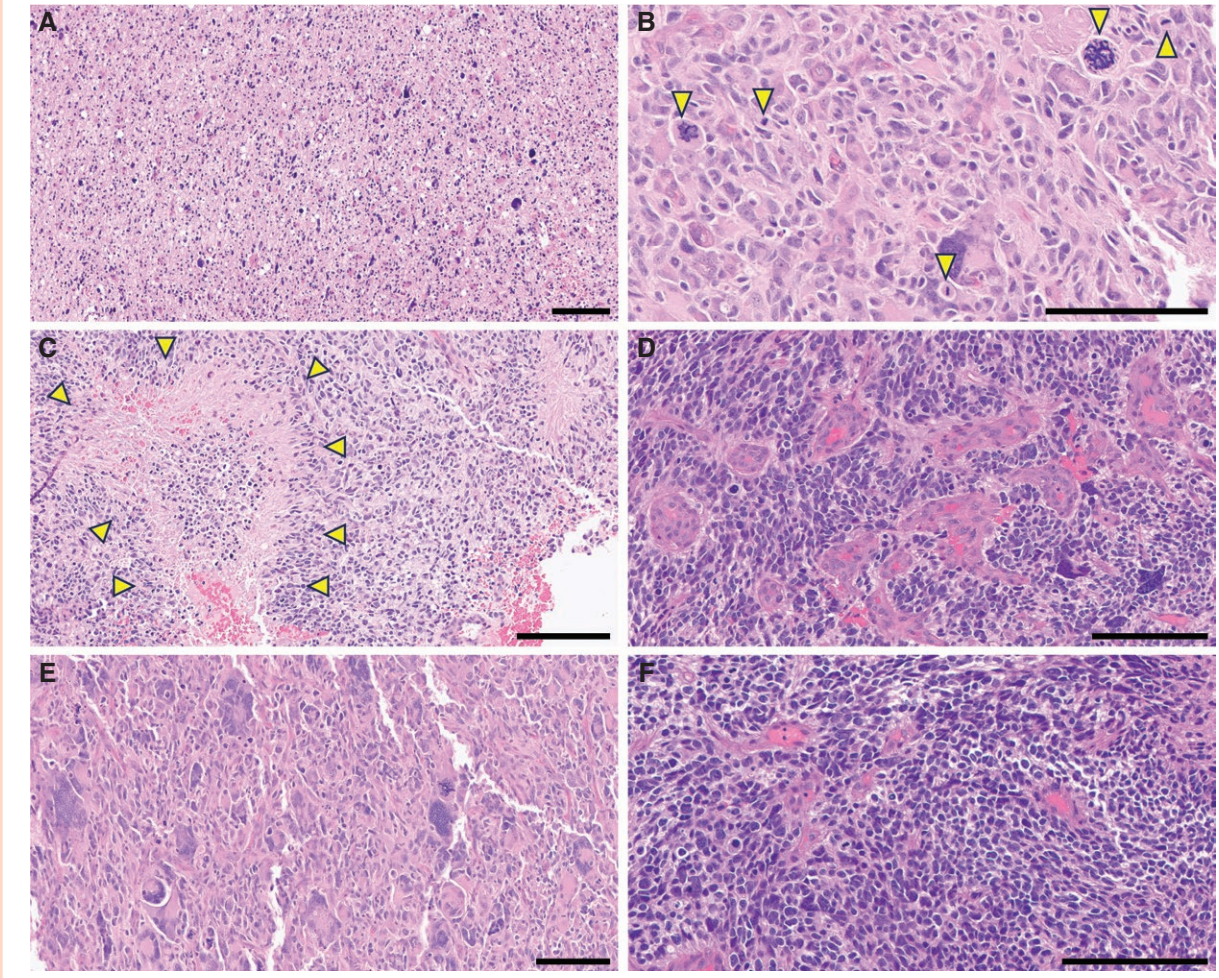

Figure 2. Representative hematoxylin and eosin-stained histologic features of diffuse midline glioma, H3 G34-mutant. (A) The glial component demonstrates single cell infiltration, characteristic of a diffuse glioma. (B) These gliomas can have elevated mitotic activity (arrowheads). Glioblastoma-like histologic features including (C) palisading necrosis (arrowheads) and (D) microvascular proliferation may be present. (E) The neoplastic glial cells frequently demonstrate giant cell cytomorphology with multinucleation. (F) These tumors commonly have an embryonal component composed of primitive appearing cells. All scale bars are at 150 μm.

between DNA sequencing and immunohistochemistry reported up to 17%), indicating that alternative methods for mutation detection (DNA sequencing or DNA whole-genome methylation) are more robust for making the diagnosis of DHG G34-mutant.[26]

Molecular Mechanistic Understanding of DHG H3 G34-Mutant

After reviewing 220 articles for the final analysis, it was found that 47 of them were based solely on in vitro studies,

while 5 articles focused on in vivo research. Additionally, 11 articles included a combination of both in vitro and in vivo studies. Multiple studies have analyzed the specific molecular interactions present in cells with H3 G34R/V mutations. One area of focus has been to provide biochemical and nuclear magnetic resonance (NMR) structural evidence through which plant homeodomains (PHDs), particularly receptors for activated c-kinase 7 (RACK7), recognize H3 G34-mutant peptides.[27] Specifically, Jiao et al., proposed that the binding of RACK7 to H3.3G34R plays a role in suppressing the transcription of CIITA, the master regulator of major histocompatibility complex (MHC) class II molecules necessary for the activation of the MHC class II immune pathway.[28] Another area of focus has been to explore interactions between H3 G34R and KDM4B, a key demethylase inactivated in alternative lengthening of telomeres (ALT) pathways, which is one pathway contributing to the proliferative nature of cancer cells.[29]These findings suggest that H3.3G34R and RACK7 complex and/or H3.3G34R binding to KDM4B could be part of the molecular mechanism by which H3.3G34R promotes cancer and regulates the immune system.

Approximately, 84 studies have provided insights into genetic alterations and molecular pathways that are crucial for targeted therapies of DHG. Chen et al. highlighted the association between DHG H3 G34-mutant and DMG H3 K27-altered demonstrating the increased NOTCH signaling, which is a pathway that selectively inhibits H3.3-mutant cell growth and is crucial for neurodevelopmental processes.[30]They found that this increase in NOTCH signaling is caused by the abnormal depression of genes through impaired H3K27me3 (trimethylation) deposition at super-enhancers in H3.3-mutant cells; specifically for H3 K27-altered.[30] In addition, Haase et al. demonstrated that H3 G34R impaired the DNA damage response, reduced chromatic accessibility, and enhanced immune-stimulatory cytokines.[31] By treating genetically engineered de novo H3 G34R mice with a combination of radiotherapy, and DNA damage response inhibitors, long-term survival was achieved in ~50% of the mice.[31] Understanding molecular interaction between H3 G34R and other molecules is critical to understanding the mechanism for HGGs. However, the clinical significance of these interactions targeting genetic alterations and molecular pathways hindering cancer promotion is understudied.

DHG G34-Mutant Tumor Microenvironment

The significance of the tumor microenvironment concerning DHG G34-mutant, particularly in the context of DNA repair mechanisms, is pivotal. In the study conducted by Haase et al., a syngeneic, genetically engineered mouse model (GEMM) along with human DHG G34-mutant cell xenografts were employed to elucidate the impact of this mutation on DNA repair pathways.[31] Their findings revealed that the G34R mutation resulted in the downregulation of DNA repair pathways, leading to genetic instability.[8] This instability manifested as the accumulation of extrachromosomal DNA, triggering activation of the cyclic GMP–AMP synthase/stimulator of interferon (IFN) genes (cGAS/STING) pathway, subsequently inducing the secretion of immune-stimulatory cytokines.[31] The therapeutic benefit of cytokine release substantiates the role of the adaptive immune response. Recent findings from Mancarella et al. provide support for this mechanism of immune regulatory cytokine release induced by the presence of unrepaired DNA and an immunepremisive immune microenvironment. These studies further highlight the potential therapeutic advantages of combining radiotherapy and immunotherapy for patients with DHG G34-mutant tumors.[32]

Furthermore, DHG G34-mutant has been associated with a distinct immune signature, such as an increase in the infiltration by antigen-presenting cells, natural killer cells, B lineage cells, decreased immunesupressive myeloid cells, and hypomethylated immune-related gene signatures.[33,34] Mutations that influence immune response, such as MUC16 mutations, have been correlated with a more favorable diagnosis, perhaps due to higher immune infiltration and response.[14] Recent studies by Andrade et al. describe abundant mature myeloid populations (resident microglia, bone marrow derived macrophages, and monocytes) in the tumor microenvironment of both histone-mutated gliomas, yet limitations were evident with small sample sizes for G34-mutant gliomas.[35] Despite the critical role of the tumor and immune microenvironment, limited literature exists regarding therapeutic strategies that harness the immune microenvironment within and among these tumors.

Biological Comparison of DHG G34-Mutant and DMG K27-Altered

The mutation in histone 3 at position 27 from lysine to methionine (H3K27M) is present in ~80% of pediatric DMGs and presents a dismal prognosis.[12,15,16,36] For H3K27M, the vast majority of mutations occur in H3-3A encoding for histone 3.3 (H3.3K27M) with fewer mutations being present for several genes that encode for histone 3.1 or histone 3.2.[6,37–41] Survival data vary by study and cohort, but generally, H3K27M has increased disease progression and lower median survival compared to DHG G34-mutant.[15,42–45] One reason survival may be worse in H3 K27M is because of anatomical location, as DMG K27M-altered often occurs in the brainstem while DHG G34-mutant are present as supratentorial non-midline tumors.[46–48] This cortical location difference allows for more ease with surgical resection. DMG H3 K27-altered presents as a distinct tumor subtype with a recognizable genetic landscape. Particularly, H3 K27M causes a global reduction in H3K27 trimethylation (H3 K27me3) mark through its inhibitory affinity for the methyltransferase enzymatic subunit, while DHG G34-mutant alters methylation patterns locally through the H3K36 trimethylation mark.[49,50] There are also key molecular differences often observed, as DHG G34-mutant show relatively increased Ki-67 indexes, changes in ALT, H3.3 recruitment, and recurrent mutations in TP53, ATRX, and cell-cycle-related components when compared with DMG K27-altered.[45,51–54] H3K27M tumors, however, have commonly gained protein oncohistone interactions, and increased expression of glucose transporter GLUT3, glycolytic enzymes, and radial glia biology

gene expression, as well as increased mutations in tumor suppression gene NF1 and oncogene PIK3CA/PIK3R1 compared with DHG G34-mutant.[45,55–57]

Despite the differences between the H3K27M and H3.3G34R/V mutations, key similarities do exist that can be utilized for optimizing our understanding of the tumors and treatment. Both DMG K27-altered and DHG G34-mutant are rapidly progressive, H3 impacted have a poor prognosis with higher risks for treatment relapse. Additionally, the mutations present in the highly conserved *N*-terminus of the TP53 gene; which is paramount for regulation of cell proliferation.[13,15,51,58] However, it is important to note that in the DMG K27-altered, the presence of TP53 mutation is associated with poorer patient survival but has been reported to have no, to little influence on DHG G34-mutant survival.[36] Interestingly, in both H3K27M and H3.3G34R/V tumors, there are increases in the NOTCH signaling pathway, which is known to regulate neurogenesis, proliferation, and apoptosis, and this is believed to contribute to overall tumorigenesis.[29,57,59]

Clinical Understanding of H3.3G34R/V Tumors

Of the 220 articles that were included in the final analysis, 71 detailed original clinical data. Among the 69 studies identified for their clinical datasets, 21 investigations employed contemporary sequencing methodologies to further investigate molecular mechanisms governing treatment resistance in DHG G34-mutant, and 2 contained data from a novel clinical trial. The age range of patients across all clinical studies varied from 0 to 85 years old (23.9 years old median age), with a median overall survival of 14.9 months. Predominant neuroanatomical sites for DHG G34-mutant were cerebral hemispheres. Enhanced treatment resistance and the mutational burden have widely been observed in DHG G34-mutant. Notably, a study employing next-generation DNA whole-genome methylation profiling, and histological analysis revealed that recurrent or progressive DHG G34-mutant exhibited heightened posttreatment deficiency in DNA mismatch repair proteins and increased tumor mutational burden.[60] The distinct mutational profile of DHG G34-mutant is further demonstrated in several molecular studies that cite heightened mutations in *PDGFRA*.[14,45,61,62] Furthermore, Williams et al. noted an increased prevalence of PDGFRA mutations in DHG G34-mutant compared to DMG K27-altered, emphasizing PDGFRA as a potentially targetable alteration in ~20% of DHG G34-mutant. This finding is substantiated by analyses demonstrating 80–100% notable occurrence of PDGFRA mutations.[14,62] Like PDGFRA, additional membrane proteins and signal transducers, namely *B7H3* and STAT3, have been recognized as potential therapeutic targets within the context of DHG G34-mutant.[45] Interestingly, the association of variants in *BRAF*, *IDH1*, *IDH2*, and *TERT* genes among H3.3G34 mutations is also heavily discussed in varied research studies.[45,63] However, in Buccoliero et al., these genes were relatively infrequent upon gene panel analysis of DHG G34-mutant.[63] Moreover, Williams et al. reported *BRAF* and *TERT* were among the most frequent genomic alterations in DMG K27-altered and DHG G34-mutant.[45] This potentially nods to variable expressivity of telomerase maintenance and RAS/MAPK pathway activity in H3.3G34R/V mutant gliomagenesis and progression. Additionally, Hwang et al. described the clinical heterogeneity in the diagnosis of children diagnosed with G34R/V gliomas noted by the Children's Oncology Group phase III prospective trial of medulloblastoma, supratentorial primitive neuroectodermal tumors (PNETs), and pineoblastoma. They found that while 6 of the 60 methylation profiled cases of PNETs had a molecular diagnosis of H3F3A/G34, 3 of the 6 had histologic features of PNET/neuroblastic architecture.[64] This further suggests the need for molecular testing to assist with disease classification so as to optimize future prospective studies.

Through retrospective investigations, 53 patients with DHG, G34-mutant brain MRIs (compared with IDH-WT GBM), confirmed predominant locations of parietal and temporal lobes and mild or no contrast enhancement of large tumor size. Despite small patient numbers, Shao et al. described distinct radiomic features that require further evaluations to ensure predictive and prognostic value for future clinical trials.[65]

Treatment for DHG G34-Mutant

Clinical trials.—A scarcity of DHG G34-mutant-focused clinical trials was evident in the literature, with a few trials identified that molecularly classified the inclusion of these patients.[30,64,66] These findings underscore the need for further innovative clinical exploration into the specific therapeutic management of these tumors. Within one of these clinical studies, pediatric patients diagnosed with HGGs and diffuse intrinsic pontine gliomas (DIPG) received bevacizumab-based therapy.[66] Notably, among patients harboring HGGs, the study yielded promising outcomes, with a 3-year progression-free survival and increased quality of life scores over the study course. The most common ≥ grade III toxicities observed were lymphopenia, neutropenia, and leukopenia. Two patients experienced grade III hypertension, while there were no occurrences of intracranial hemorrhages. Overall, this suggests that bevacizumab-based therapy may represent a tolerable alternative to the conventional temozolomide (TMZ) regimen.[66] Nonetheless, the study incorporated only a small number of DHG G34-mutant, which restricts the extrapolation of these findings specifically for this patient population. Another progressive study referenced in Haase et al. utilized a PARP inhibitor veliparib with temozolomide to treat non-brainstem pHGG. However, this study was terminated early because of poor clinical outcomes which failed to stratify for DHG G34-mutant.[31] In the HERBY Phase II multicenter trial, newly diagnosed non-brainstem HGGs were randomly assigned to either standard of care (temozolomide and radiotherapy postsurgical resection) or standard of care in addition to bevacizumab. Although bevacizumab did not result in better overall survival, 7 out of 89 tumors were identified as G34 mutant. Those patients with G34-mutant disease experienced a shorter median event-free survival of 8.3 months compared to 11.3 months in the wild-type group mc.[15,67]

Additionally, Karschnia et al. recently detailed the importance of maximal surgical resection for patients with

IDH-WT newly diagnosed glioblastoma.[68] While they did not further delineate optimal surgery for patients with DHG G34-mutant, through evaluating 1021 glioblastoma patients, over several centers, they concluded that low residual tumor volumes and extent of resection of non-contrast enhancing tumors (≤5 cm^3 residual) were linked to optimized survival times; noting that supramaximal resection of contrast-enhancing tumor areas were most advantageous.

Standard treatment of malignant brain tumors includes radiation therapy, yet little is understood about the intricacies of radiotherapy dose effect on G34R/V glioma vs. other high-grade cortical gliomas. Specifically, examining the effectual difference of radiotherapy on histone mutated gliomas, Knight et al. found that H3.3G34 tumors had less volumetric reductive responses than H3K27M tumors 3 months post radiotherapy.[58] Of the 7 patients evaluated with H3.3G34R disease, the majority of patients demonstrated distant only or both local and distant disease recurrent sites. Upcoming immunotherapy trials of DHG G34-mutant focusing on immune-checkpoint inhibition therapies and immune-specific stratification, along with a combination of chemotherapy that stimulates the immune system via cGAS/STING pathway activation, are promising therapeutic interventions for this devastating pediatric brain cancer.[31,33] As evidenced collectively by these studies, there exist no standard treatment regimens used across varied clinical centers. Despite these limited findings, there have been no prospective studies conducted that delineate consensus on treatment regimens at the time of initial diagnosis or disease progression (including the degree of surgical resection and radiotherapy), rate and location of disease relapse/progression, or overall/progression-free survival rates for such an aggressive disease. In preclinical studies aimed at examining distinct vulnerabilities of DHG, G34-mutant, Liu et al. demonstrated the potential benefit from cyclin-dependent kinase inhibitor 4/6 inhibitor, ribociclib. In one patient with progressive disease, post 2 different radio/chemotherapy treatment regimens, ribociclib therapy was given for compassionate use and found to provide a survival benefit of 17 months.[25]

Treatments Targeting Gene Regulation and Molecular Pathways

Previous HGG-focused studies have included targeting PDGFRA, a gene frequently mutated and present in one-fifth of DHG G34-mutant and DMG K27-altered.[45] Notably, Hu et al. suggested that PDGFRA mutation may indicate poor prognosis in DHG G34-mutant because of their promotion in the oncogenic signaling cascade.[14]

Another research area has focused on exploring pathways regulated by the H3.3G34R/V mutation as a promising target for future targeted therapies. Bjerke et al. explored the upregulation of MYCN (neuroblastoma-derived v-myc avian myelocytomatosis), a viral-related oncogene giving rise to incurable cerebral hemispheric glioblastoma when expressed in the correct developmental context. Their research focused on the possibility of stabilizing MYCN protein through synthetic lethality in DHG G34-mutant.[69] Additionally, researchers have investigated the regulation of MYCN via MAPK/ERK activation signaling in an attempt to treat DHG G34-mutant, with the added intent to increase the permeability of the BBB.[70]

Another study found that mutations in the core histone exhibited greater sensitivity to several repurposed and/or cancer drugs. Bonner et al. explored epithelial growth factor receptor (EGFR) inhibitors (neratinib and pelitinib) targeting the EGFR pathway, a cell growth pathway.[71] Their study showed that alterations in cell-cycle pathway components are more frequently found in DHG G34-mutant (27%) than in DMG K27-altered (9%), which may make them more sensitive to cyclin-dependent kinase inhibitors such as palbociclib and abemaciclib.[71]

Therapies Targeting the Epigenome

Targeting the epigenome establishes windows of opportunity for potential oncogenic co-option of the *cis*-regulatory landscape, as recently shown for DHG G34-mutant.[72] As altered chromatin states may be reversible, an improved understanding of aberrant cancer epigenomes could inform the design of effective therapies.[72] Other researchers have evaluated patients with DHG G34-mutant, and their outcome appears associated with a higher response rate to glioblastoma standard of care including temozolomide, which specifically depends on MGMT promoter methylation status.[26] Collectively, these studies point to the idea that future research warrants the development of therapies and better technologies that target the genomic instability through DNA damage repair processes and the regulation of genes associated with cell fate decisions.[8] Giacomini et al. describe how aberrant DNA repair of S phase DNA damage within these tumors disturbs genome integrity. Specifically, they found that inhibition of the DNA repair enzyme polynucleotide kinase 3′-phosphatase (PNKP) results in tumor growth arrest and lack of misrepair of DNA damage.[73] Yet further studies are required with in vivo models to examine the use of such agents to be delivered into the CNS combined with radio/chemotherapy.

Given that both, DMG K27-altered and DHG G34-mutant share key molecular similarities, previous studies have investigated treating both tumor types with the same promising compounds. Mota et al. explored the utility of AU15330, a compound that disrupts the oncogenic master chromatin remodeling switch/sucrose nonfermentable complex via SMARCA2/4 and PBRM1 degradation.[74] They found that H3K27M mutant cells exhibited increased SMARCA2/4 and PBRM1 compared to H3 G34V mutant cells.[74] In line with these findings, H3 K27M-mutant cells demonstrated increased cell death sensitivity to AU15330.[74] Another study investigated the utility of GSKJ4, a pharmacological inhibitor of K27 demethylase, and concluded that GSKJ4 treatment had a dose-dependent inhibition for cell viability and clonal growth of H3 K27M mutant cells, but not H3 G34V mutant cells.[49] Interestingly, additional researchers found 3 distinct compounds that exhibited significant cell death on both H3 K27M-mutant and H3 G34R-mutant cells—chaetocin, an inhibitor of H3K9 methyltransferases (SUV39H1/2, and EHMT1/2) and BRM014, an ATPase inhibitor of SMARCA4/2 and a peptidomimetic lead compound, KL-1,

that disrupts transcription elongation.[57,75,76] Khazaei et al. found that H3 G34 substitutions influence motor functions, neurodevelopmental stunting, and neurodegeneration resulting in DNA methyltransferase (DNMT3A) recruitment. These changes to the DNA methylation profile were linked to increased inflammation, poor immune activation, and neuronal dysregulation.[34] Additional studies have described the role that H3.3G34R mutations play in the epigenome, specifically in chromatin remodeling related to oncogenesis and treatment resistance.[29,77]

Discussion

Collectively, the 220 articles that included or focused on DHG G34-mutant identified by our scoping review have detailed the diagnostic features, understanding of pathogenesis to date and treatment resistance, yet there remain intrinsic complexities of this tumor subtype that are yet not fully understood. DHG G34-mutant remains challenging to treat despite multi-modality therapy which can be associated with many long-term side effects. Thus, identifying targeted therapies that penetrate the BBB while conforming to the genomic and epigenetic features of DHG G34-mutant is a significant obstacle that needs to be overcome. Overall, there is an urgent need for more DHG G34-mutant studies focusing on (1) determining the tumor microenvironmental differences, (2) identifying additional molecular phenotypes, (3) uncovering novel BBB permeable targeted approaches, and (4) testing the efficacy of varied precision therapies which can be translated intelligently to prospective clinical trials.

Limitations

This scoping review summarizes the published data regarding known molecular mechanisms governing treatment resistance in DHG G34-mutant and the use of innovative techniques, such as next-generation sequencing, DNA whole-genome methylation, and multiplex immunohistochemistry for identifying tumor cells–immune cell interactions within the tumor microenvironment. While the literature on clinical trials for DHG G34-mutant is scarce, with few trials identified that incorporated patients with DHG G34-mutant, Hummel et al. trial yielded promising outcomes for bevacizumab-based therapy as a tolerable adjunct to conventional temozolomide regimens. Yet patients harboring the H3.3G34 mutation require a larger population of patients with DHG G34-mutant to solidify clinical decision making towards quality of life enhancing therapy.[66] Thus, further innovative clinical exploration is most needed to manage DHG G34-mutant recurrence and known resistance to standard therapy.

The treatment of DHG G34-mutant poses a significant challenge due to the presence of the blood–brain barrier (BBB), which limits the effectiveness of many cancer drugs from entering the CNS. Finding ways to overcome the BBB's selective permeability is critical to improving the therapeutic outcomes of chemotherapy for HGG patients. Only 2 out of the 220 papers included in this scoping review referenced the BBB and its restrictive nature. While these studies highlighted various approaches, such as using small molecule chemotherapeutic drugs like tyrosine kinase inhibitors and arterial spin labeling to assess intra-tumoral microvascular blood flow, to bypass the BBB, there are still many unknowns about the optimal means to enhance BBB permeability for the treatment of DHG G34-mutant.[78,79]

Concluding Remarks

This scoping review of DHG G34-mutant has examined published research detailing in vitro and in vivo research advancements, clinical diagnostics, and numerous directed treatment responses. This literature collectively demonstrates the involvement of numerous oncogenes and tumor suppressor genes involved in RAS/MAPK, MYCN, NOTCH, and LIF/STAT pathways, such as *ATRX*, *PDGFRA*, and *TP53* which have been shown to influence neural characteristics and prognostic tumor outcomes. While certain therapeutic modalities, including H3K9 methyltransferase inhibitors, DNA damage response inhibitors, STING agonists, and bevacizumab-based therapies, have exhibited preclinical efficacy and some indication of positive clinical outcomes, more research on agents that permeate the BBB to impair growth is necessary. Additionally, further research into the supportive role of the tumor microenvironment that enables disease progression is warranted. Collectively, these studies will empower prospective clinical trials using DHG G34-mutant targeted therapies which could enhance disease survival.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

brain cancer | glioblastoma | glioma | H3.3G34R/V | H3F3

Funding

This research/work/investigator was supported by the Division of Intramural Research of the National Institutes of Health (NIH) and the National Institute of Neurologic Disorders and Stroke (NINDS). The content is solely the responsibility of the author(s) and does not necessarily represent the official views of the NIH.

Acknowledgments

This work was supported by the NINDS Intramural Research Program. We would like to thank Gisela Butera, biomedical librarian at the NIH library, for their assistance with the scoping

review methodology and designing and conducting the literature searches.

Conflict of interest statement

None declared.

Authorship statement

K.T., M.C., T.M., and S.J. contributed to the manuscript design. K.T., M.C., T.M., M.G.C., and S.J. analyzed the manuscripts and interpreted the findings. All authors have contributed to the manuscript and read and approved the final version.

Data availability

Data will be shared at the time of publication or shortly thereafter.

Affiliations

Developmental Therapeutics and Pharmacology Unit, Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke (NINDS), NIH, Bethesda, Maryland 20892, USA (K.T., M.C., T.M., S.J.); Neuropathology Unit, Surgical Neurology Branch, National Institute of Neurologic Disorders and Stroke (NINDS), NIH, Bethesda, Maryland 20892, USA (P.J.C.); Brain Tumor Research and Translational Neuro-Oncology Lab, Department of Neurosurgery, Department of Cell and Developmental Biology, University of Michigan, Ann Arbor, Michigan 48109, USA (M.G.C.)

References

1. Cunningham RM, Walton MA, Carter PM. The major causes of death in children and adolescents in the United States. *N Engl J Med.* 2018;379(25):2468–2475.
2. Sweha SR, Chung C, Natarajan SK, et al. Epigenetically defined therapeutic targeting in H3.3G34R/V high-grade gliomas. *Sci Transl Med.* 2021;13(615):eabf7860.
3. Maeda S, Ohka F, Okuno Y, et al. H3F3A mutant allele specific imbalance in an aggressive subtype of diffuse midline glioma, H3 K27M-mutant. *Acta Neuropathol Commun.* 2020;8(1):8.
4. Park S-M, Choi E-Y, Bae M, et al. Histone variant H3F3A promotes lung cancer cell migration through intronic regulation. *Nat Commun.* 2016;7(1):12914.
5. Weinberg DN, Allis CD, Lu C. Oncogenic mechanisms of histone H3 mutations. *Cold Spring Harb Perspect Med.* 2017;7(1):a026443. 10.1101/cshperspect.a026443
6. Alencastro Veiga Cruzeiro G, Rota C, Hack OA, Segal R, Filbin MG. Understanding the epigenetic landscape and cellular architecture of childhood brain tumors. *Neurochem Int.* 2021;144:104940.
7. Lavrador JP, Reisz Z, Sibtain N, et al. H3 G34-mutant high-grade gliomas: integrated clinical, imaging and pathological characterisation of a single-centre case series. *Acta Neurochir (Wien).* 2023;165(6):1615–1633.
8. Caeiro LD, Verdun RE, Morey L. Histone H3 mutations and their impact on genome stability maintenance. *Biochem Soc Trans.* 2024;52:2179–2191.
9. Aziz-Bose R, Monje M. Diffuse intrinsic pontine glioma: molecular landscape and emerging therapeutic targets. *Curr Opin Oncol.* 2019;31(6):522–530.
10. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro-Oncology.* 2021;23(8):1231–1251.
11. Louis DN, Wesseling P, Aldape K, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020;30(4):844–856.
12. Picart T, Barritault M, Poncet D, et al. Characteristics of diffuse hemispheric gliomas, H3 G34-mutant in adults. *Neurooncol Adv.* 2021;3(1):vdab061.
13. Crowell C, Mata-Mbemba D, Bennett J, et al. Systematic review of diffuse hemispheric glioma, H3 G34-mutant: outcomes and associated clinical factors. *Neurooncol Adv.* 2022;4(1):vdac133.
14. Hu W, Duan H, Zhong S, Zeng J, Mou Y. High frequency of PDGFRA and MUC family gene mutations in diffuse hemispheric glioma, H3 G34-mutant: a glimmer of hope? *J Transl Med.* 2022;20(1):64.
15. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell.* 2017;32(4):520–537.e5.
16. Huchedé P, Leblond P, Castets M. The intricate epigenetic and transcriptional alterations in pediatric high-grade gliomas: targeting the crosstalk as the oncogenic Achilles' heel. *Biomedicines.* 2022;10(6):1311.
17. Lucas CG, Mueller S, Reddy A, et al. Diffuse hemispheric glioma, H3 G34-mutant: genomic landscape of a new tumor entity and prospects for targeted therapy. *Neuro-Oncology.* 2021;23(11):1974–1976.
18. Argersinger DP, Rivas SR, Shah AH, Jackson S, Heiss JD. New developments in the pathogenesis, therapeutic targeting, and treatment of H3K27M-mutant diffuse midline glioma. *Cancers (Basel).* 2021;13(21):5280.
19. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 2005;8(1):19–32.
20. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5(69):69.
21. Peters M, Marnie C, Tricco A, et al. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth.* 2020;18(10):3.
22. Sturm D, Orr BA, Toprak UH, et al. New brain tumor entities emerge from molecular classification of CNS-PNETs. *Cell.* 2016;164(5):1060–1072.
23. Korshunov A, Capper D, Reuss D, et al. Histologically distinct neuroepithelial tumors with histone 3 G34 mutation are molecularly similar and comprise a single nosologic entity. *Acta Neuropathol.* 2016;131(1):137–146.
24. Aboubakr O, Métais A, Maillard J, et al. Utility of combining OLIG2 and SOX10 IHC expression in CNS tumours: promising biomarkers for subtyping paediatric- and adult-type gliomas. *Histopathology.* 2024;84(5):893–899.
25. Liu I, Alencastro Veiga Cruzeiro G, Bjerke L, et al. GABAergic neuronal lineage development determines clinically actionable targets in diffuse hemispheric glioma, H3G34-mutant. *Cancer Cell.* 2024;42:1528–1548.e17.
26. Gianno F, Antonelli M, Di Dio T, et al. Correlation between immunohistochemistry and sequencing in H3G34-Mutant Gliomas. *Am J Surg Pathol.* 2021;45(2):200–204.

27. Lan WX, Li Z, Jiao FF, et al. Structural Basis of RACK7 PHD domain to read a pediatric glioblastoma-associated histone mutation H3.3G34R. *Chin J Chem.* 2021;39(9):2433–2440.
28. Jiao F, Li Z, He C, et al. RACK7 recognizes H3.3G34R mutation to suppress expression of MHC class II complex components and their delivery pathway in pediatric glioblastoma. *Sci Adv.* 2020;6(29):eaba2113.
29. Udugama M, Hii L, Garvie A, et al. Mutations inhibiting KDM4B drive ALT activation in ATRX-mutated glioblastomas. *Nat Commun.* 2021;12(1):2584.
30. Chen KY, Bush K, Klein RH, et al. Reciprocal H3.3 gene editing identifies K27M and G34R mechanisms in pediatric glioma including NOTCH signaling. *Commun Biol.* 2020;3(1):363.
31. Haase S, Banerjee K, Mujeeb AA, et al. H3.3-G34 mutations impair DNA repair and promote cGAS/STING-mediated immune responses in pediatric high-grade glioma models. *J Clin Invest.* 2022;132(22):e154229.
32. Mancarella D, Ellinghaus H, Sigismondo G, et al. Deposition of onco-histone H3.3-G34W leads to DNA repair deficiency and activates cGAS/STING-mediated immune responses. *Int J Cancer.* 2024;154(12):2106–2120.
33. Bockmayr M, Klauschen F, Maire C L, et al. Immunologic profiling of mutational and transcriptional subgroups in pediatric and adult high-grade gliomas. *Cancer Immunol Res.* 2019;7(9):1401–1411.
34. Khazaei S, Chen CCL, Andrade AF, et al. Single substitution in H3.3G34 alters DNMT3A recruitment to cause progressive Neurodegeneration. *Cell.* 2023;186(6):1162–1178.e20.
35. Andrade AF, Annett A, Karimi E, et al. Immune landscape of oncohistone-mutant gliomas reveals diverse myeloid populations and tumor-promoting function. *Nat Commun.* 2024;15(1):7769.
36. Vuong HG, Le HT, Dunn IF. The prognostic significance of further genotyping H3G34 diffuse hemispheric gliomas. *Cancer.* 2022;128(10):1907–1912.
37. Badodi S, Marino S. Epigenetic mechanisms in paediatric brain tumours: regulators lose control. *Biochem Soc Trans.* 2022;50(1):167–185.
38. Bočkaj I, Martini TEI, de Camargo Magalhães ES, et al. The H3.3K27M oncohistone affects replication stress outcome and provokes genomic instability in pediatric glioma. *PLoS Genet.* 2021;17(11):e1009868.
39. Diaz AK, Baker SJ. The genetic signatures of pediatric high-grade glioma: no longer a one-act play. *Semin Radiat Oncol.* 2014;24(4):240–247.
40. Lee J, Solomon DA, Tihan T. The role of histone modifications and telomere alterations in the pathogenesis of diffuse gliomas in adults and children. *J Neurooncol.* 2017;132(1):1–11.
41. Qiu L, Hu X, Jing Q, et al. Mechanism of cancer: oncohistones in action. *J Genet Genomics.* 2018;45(5):227–236.
42. Cantero D, Rodríguez de Lope A, Moreno de la Presa R, et al. Molecular study of long-term survivors of glioblastoma by gene-targeted next-generation sequencing. *J Neuropathol Exp Neurol.* 2018;77(8):710–716.
43. Korshunov A, Ryzhova M, Hovestadt V, et al. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. *Acta Neuropathol.* 2015;129(5):669–678.
44. Synhaeve NE, van den Bent MJ, French PJ, et al. Clinical evaluation of a dedicated next generation sequencing panel for routine glioma diagnostics. *Acta Neuropathol Commun.* 2018;6(1):126.
45. Williams EA, Brastianos PK, Wakimoto H, et al. A comprehensive genomic study of 390 H3F3A-mutant pediatric and adult diffuse high-grade gliomas, CNS WHO grade 4. *Acta Neuropathol.* 2023;146(3):515–525.
46. Gerges N, Fontebasso AM, Albrecht S, Faury D, Jabado N. Pediatric high-grade astrocytomas: a distinct neuro-oncological paradigm. *Genome Med.* 2013;5(7):66.
47. Lazow MA, Leach JL, Trout AT, et al. Extraneural metastases of diffuse midline glioma, H3 K27M-mutant at diagnosis: case report, review of the literature, and identifying targetable alterations. *J Pediatr Hematol Oncol.* 2022;44(2):e597–e604.
48. Ocasio JK, Budd KM, Roach JT, Andrews JM, Baker SJ. Oncohistones and disrupted development in pediatric-type diffuse high-grade glioma. *Cancer Metastasis Rev.* 2023;42(2):367–388.
49. Hashizume R, Andor N, Ihara Y, et al. Pharmacologic inhibition of histone demethylation as a therapy for pediatric brainstem glioma. *Nat Med.* 2014;20(12):1394–1396.
50. Venneti S, Santi M, Felicella MM, et al. A sensitive and specific histopathologic prognostic marker for H3F3A K27M mutant pediatric glioblastomas. *Acta Neuropathol.* 2014;128(5):743–753.
51. Diaz M, Rana S, Silva Correia CE, et al. Leptomeningeal disease in histone-mutant gliomas. *Neurooncol Adv.* 2023;5(1):vdad068.
52. Minasi S, Baldi C, Gianno F, et al. Alternative lengthening of telomeres in molecular subgroups of paediatric high-grade glioma. *Childs Nerv Syst.* 2021;37(3):809–818.
53. Newhart A, Rafalska-Metcalf IU, Yang T, et al. Single cell analysis of RNA-mediated histone H3.3 recruitment to a cytomegalovirus promoter-regulated transcription site. *J Biol Chem.* 2013;288(27):19882–19899.
54. Zhao Y, Chen Y, Wang L, Gao Y, Xu J. The clinicopathological features and prognosis of multifocal high-grade gliomas in adults with H3F3A mutation. *Neurosciences (Riyadh).* 2023;28(1):42–47.
55. Bayliss J, Mukherjee P, Lu C, et al. Lowered H3K27me3 and DNA hypomethylation define poorly prognostic pediatric posterior fossa ependymomas. *Sci Transl Med.* 2016;8(366):366ra161.
56. Chung C, Sweha SR, Pratt D, et al. Integrated metabolic and epigenomic reprograming by H3K27M mutations in diffuse intrinsic pontine gliomas. *Cancer Cell.* 2020;38(3):334–349.e9.
57. Siddaway R, Canty L, Pajovic S, et al. Oncohistone interactome profiling uncovers contrasting oncogenic mechanisms and identifies potential therapeutic targets in high grade glioma. *Acta Neuropathol.* 2022;144(5):1027–1048.
58. Knight A, Horsley P, Yuile A, et al. Volumetric response and pattern of failure of histone altered high grade glioma in adults following management with radiation therapy. *J Neurooncol.* 2023;163(1):281–288.
59. Funato K, Smith RC, Saito Y, Tabar V. Dissecting the impact of regional identity and the oncogenic role of human-specific NOTCH2NL in an hESC model of H3.3G34R-mutant glioma. *Cell Stem Cell.* 2021;28(5):894–905.e7.
60. Wood MD, Beadling C, Neff T, et al. Molecular profiling of pre- and post-treatment pediatric high-grade astrocytomas reveals acquired increased tumor mutation burden in a subset of recurrences. *Acta Neuropathol Commun.* 2023;11(1):143.
61. De Cola A, Foss A, Gilbertson R, Pathania M. Biological, diagnostic, and therapeutic insights from (Epi)Genomic profiling of pediatric brain tumors. *Ann Rev Cancer Biol.* 2024;8(Volume 8, 2024):199–226.
62. Zhang RQ, Shi Z, Chen H, et al. Biomarker-based prognostic stratification of young adult glioblastoma. *Oncotarget.* 2016;7(4):5030–5041.
63. Buccoliero AM, Giunti L, Moscardi S, et al. Pediatric high grade glioma classification criteria and molecular features of a case series. *Genes (Basel).* 2022;13(4):624.
64. Hwang EI, Kool M, Burger PC, et al. Extensive molecular and clinical heterogeneity in patients with histologically diagnosed CNS-PNET treated as a single entity: a report from the children's oncology group randomized ACNS0332 trial. *J Clin Oncol.* 2018;36(34):JCO2017764720.
65. Shao H, Gong J, Su X, et al. MRI characteristics of H3 G34-mutant diffuse hemispheric gliomas and possible differentiation from IDH-wild-type glioblastomas in adolescents and young adults. *J Neurosurg Pediatr.* 2024;33(3):236–244.
66. Hummel TR, Salloum R, Drissi R, et al. A pilot study of bevacizumab-based therapy in patients with newly diagnosed high-grade gliomas and diffuse intrinsic pontine gliomas. *J Neurooncol.* 2016;127(1):53–61.

67. Mackay A, Burford A, Molinari V, et al. Molecular, pathological, radiological, and immune profiling of non-brainstem pediatric high-grade glioma from the HERBY phase II Randomized trial. *Cancer Cell*. 2018;33(5):829–842.e5.e5.
68. Karschnia P, Young JS, Dono A, et al. Prognostic validation of a new classification system for extent of resection in glioblastoma: a report of the RANO resect group. *Neuro Oncol*. 2023;25(5):940–954.
69. Bjerke L, Mackay A, Nandhabalan M, et al. Histone H3.3 mutations drive pediatric glioblastoma through upregulation of MYCN. *Cancer Discov*. 2013;3(5):512–519.
70. Marlow C, Cuoco JA, Hoggarth AR, et al. Pediatric diffuse hemispheric glioma H3 G34-mutant with gains of the BRAF locus: an illustrative case. *Rare Tumors*. 2023;15(0):20363613231168704.
71. Bonner ER, Dawood A, Gordish-Dressman H, et al. Pan-cancer atlas of somatic core and linker histone mutations. *NPJ Genomic Med*. 2023;8(1):23.
72. Krug B, Harutyunyan AS, Deshmukh S, Jabado N. Polycomb repressive complex 2 in the driver's seat of childhood and young adult brain tumours. *Trends Cell Biol*. 2021;31(10):814–828.
73. Giacomini G, Piquet S, Chevallier O, et al. Aberrant DNA repair reveals a vulnerability in histone H3.3-mutant brain tumors. *Nucleic Acids Res*. 2024;52(5):2372–2388.
74. Mota M, Sweha SR, Pun M, et al. Targeting SWI/SNF ATPases in H3.3K27M diffuse intrinsic pontine gliomas. *Proc Natl Acad Sci USA*. 2023;120(18):e2221175120.
75. Katagi H, Takata N, Aoi Y, et al. Therapeutic targeting of transcriptional elongation in diffuse intrinsic pontine glioma. *Neuro Oncol*. 2021;23(8):1348–1359.
76. Mo Y, Duan S, Zhang X, et al. Epigenome programming by H3.3K27M mutation creates a dependence of pediatric glioma on SMARCA4. *Cancer Discov*. 2022;12(12):2906–2929.
77. Voon HPJ, Udugama M, Lin W, et al. Inhibition of a K9/K36 demethylase by an H3.3 point mutation found in paediatric glioblastoma. *Nat Commun*. 2018;9(1):3142.
78. Cabral de Carvalho Corrêa D, Tesser-Gamba F, Dias Oliveira I, et al. Gliomas in children and adolescents: investigation of molecular alterations with a potential prognostic and therapeutic impact. *J Cancer Res Clin Oncol*. 2022;148(1):107–119.
79. Kitakami K, Beppu T, Sato Y, Kurose A, Ogasawara K. Utility of arterial spin labeling for objective assessment of intratumoral microvessels in diffuse hemispheric glioma, H3 G34R-mutant: a case report and literature review. *Radiol Case Rep*. 2023;18(3):856–861.