Journal of Neuro-Oncology (2022) 158:405–412
https://doi.org/10.1007/s11060-022-04027-2

REVIEW

The prognostic significance of *HIST1H3B/C* and *H3F3A* K27M mutations in diffuse midline gliomas is influenced by patient age

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Received: 29 March 2022 / Accepted: 5 May 2022 / Published online: 23 May 2022

Abstract

Introduction Diffuse midline gliomas (DMGs) are infiltrative midline gliomas harboring H3K27M mutations and are generally associated with poor outcomes. H3K27M mutations include mutations in *HIST1H3B/C (H3.1), HIST2H3B/D (H3.2),* or *H3F3A (H3.3)* genes. It is still unclear whether these mutations each portend a universally poor prognosis, or if there are any factors which modulate outcome. The main objective of this study was to study overall survival (OS) of *H3.1* versus *H3.3* K27M-mutant DMGs in pediatric and adult patients.

Methods PubMed and Web of Science were searched, and we included studies if they have individual patient data of DMGs with available H3K27M genotype. Kaplan–Meier analysis and Cox regression models were used to analyze the survival of *H3.1* and *H3.3* mutations in each subgroup.

Results We included 26 studies with 102 and 529 *H3.1* and *H3.3*-mutant DMGs, respectively. The *H3.1* mutation was more commonly seen in younger age. In pediatric population, *H3.3* mutation conferred a shorter survival (median OS of 10.1 vs 14.2 months; $p < 0.001$) in comparison to *H3.1*-positive patients, which was further confirmed in the multivariate Cox analysis. Conversely, *H3.3* was associated with a prolonged survival in adult patients as compared with *H3.1* mutation (median OS of 14.4 vs 1.7 months; $p = 0.019$).

Conclusion We demonstrated that the prognosis of *H3.1* and *H3.3* K27M mutation in DMG patients is modulated by patient age. Routine H3K27M mutation genotyping in newly diagnosed DMGs may further stratify patients with these difficult tumors.

Keywords Histone · H3 · H3K27M · H3F3A · HIST1H3B/C · Midline glioma

Introduction

Midline gliomas are mostly seen in children, and typically arise in the pons, thalamus, or spinal cord [1]. The Lysine 27-to-methionine (K27M) mutations, either in the *HIST1H3B/C (H3.1), HIST2H3B/D (H3.2),* or *H3F3A (H3.3)* genes, are molecularly defined by mutations in genes encoding the histone H3 [1]. There are different histone H3 proteins including the H3.3, which is expressed constitutively and throughout the cell cycle whereas the H3.1 protein is specifically expressed only during the S-phase [2]. Diffuse midline gliomas (DMG) are infiltrative tumors with a *H3* K27M mutation involving the midline structures, These mutations can be found in 80% in pediatric and 15–60% in adult patients [3–6]. DMGs portend an adverse prognosis with a typical survival of less than 1 year from diagnosis despite decades of clinical trials [7]. These tumors were thus classified as a separate entity in the 2016 and 2021 World

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Health Organization (WHO) classifications of CNS tumors [8, 9]. On the contrary, only a subset of adult patients harbored H3K27M mutations [6]. Notably, there is evidence that DMGs in adult and pediatric patients are histologically and prognostically similar [10].

Of the H3K27M mutations, *H3.3* are the most common, and are seen in about 70% of pediatric DMGs while K27M mutation in *H3.1* accounts for the remaining of cases [11, 12]. *H3.2* K27M mutations are extremely rare [11]. *H3.1* mutations, however, are relatively uncommon in adult DMGs as compared to the pediatric group [13]. Mutations in the *H3.1* and *H3.3* genes have been shown to drive two distinct oncogenic transformations with different prognoses and phenotypes [11]. However, there is a lack of clarity regarding the difference in prognosis of these mutations in the pediatric and adult populations. Hence, the primary objective of this study was to investigate this difference by integrating individual participant data of published studies on DMGs.

Materials and methods

Search strategy

Our systematic review and meta-analysis of individual participant data was in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines [14]. Two databases (PubMed and Web of Science) were systematically searched using the key words "Glioma" and "H3 K27M OR H3F3A OR HIST1H3B K27M OR H3-K27M OR H3K27M" in July 2021. A hand search of the reference list of the articles was also performed to ensure the identification of all relevant studies pertinent to the topic.

Study selection criteria

Two authors independently reviewed and selected the studies satisfying the following criteria: (i) studies on DMGs with H3K27M genotyping data available, and (ii) studies with individual patient data of H3K27M mutation. All discrepancies were reviewed and resolved by the consensus of all authors. The exclusion criteria were experimental and animal studies, books, review articles, preprints, proceeding papers, conference abstracts, and studies with duplicated data.

Data collection

The full text of each eligible article was read by two independent reviewers. The following data were extracted: authors, institution, country, year of publication, study period, H3K27M genotypes, demographic information, tumor location, WHO grades, treatments (e.g., extent of resection, radiotherapy, and chemotherapy), overall survival (OS) time, OS status, and accompanying genetic events.

Outcomes of interest

In this study, the primary outcomes of interest were all-cause mortality of *H3.1* and *H3.3* K27M DMGs in pediatric (age 0–18) and adult populations (age > 18).

Statistical analysis

Categorical data were displayed as frequency, and a comparison between groups was done using the Chi-square test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation (SD) for normal distributions and median + interquartile range for non-normal distributions. Normality was tested using skewness, kurtosis, visual inspection of the histogram, QQ plot. The t-test and Mann–Whitney U test were performed to compare differences between 2 groups for normally and non-normally distributed variables, respectively. The Kaplan–Meier curve and log-rank test were computed to analyze all-cause mortality differences between two variants (*H3.3* vs *H3.1*). A two-sided p value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) and R software, version 4.1.1 (The R Foundation, Vienna, Austria).

Results

We identified 788 articles for the title and abstract screening and 76 articles were selected for full-text review. After reading full-text, we included 26 studies with available H3K27M genotyping information comprising 102 *H3.1* and 529 *H3.3* K27M DMGs for integrated analyses (Fig. 1) [6, 11–13, 15–36]. There were two cases with *H3.2* K27M mutation which were excluded from the analyses to avoid potential bias.

The differences in patient clinical characteristics between *H3.1* and *H3.3* K27M-mutant DMGs

Table 1 presents the clinical characteristics of the *H3.1* and *H3.3* K27M-mutant DMGs. Compared to the *H3.1* K27M, the *H3.3* K27 mutation was more commonly identified in adult patients ($p < 0.001$). No gender difference was observed between the two mutations. Spinal cord more frequently harbored the *H3.3* K27M mutations whereas *H3.1* K27M-mutant tumors were limited to the brainstem.

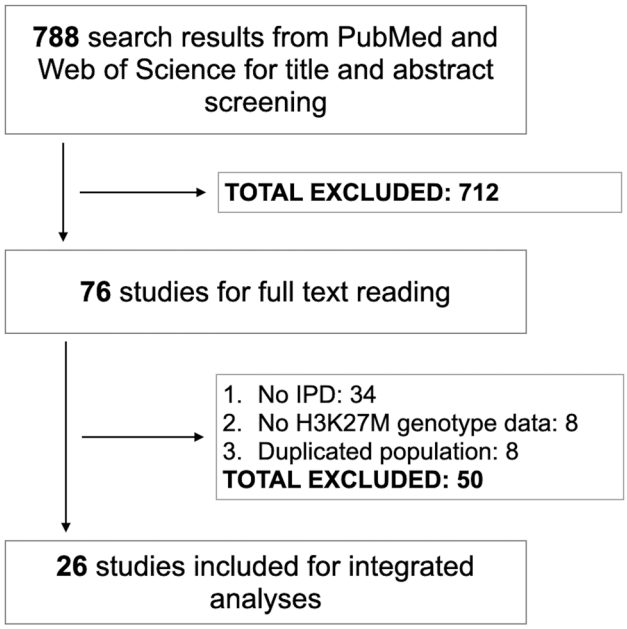

Fig. 1 Study flowchart

With respect to treatment modalities, the *H3.3* K27M variants were associated with higher rate of tumor resection (p = 0.048) and chemotherapy administration (p = 0.04), but not radiotherapy administration.

The differences in associated genetic events between *H3.1* and *H3.3* K27M-mutant DMGs

The genetic events associated with these two mutations are shown in Table 2. *ACVR1* mutations, *EGFR* amplification, and *PIK3CA* mutations were more common in *H3.1* K27M-mutant DMGs whereas *ATRX* and *TP53* mutations and *PDGFRA* amplification were associated with *H3.3*- mutated tumors.

The survival differences of H3K27M mutation genotypes in pediatric and adult patients

Overall, the median OS was less favorable in the *H3.3* K27M- than in the *H3.1* K27M-mutant DMGs (11.0 vs. 14.1 months, p < 0.001). Stratified into adult and pediatric groups, the *H3.3* K27M mutation was associated with a better survival when compared to patients harboring an *H3.1* K27M mutation in adults (median OS of 14.4 vs 1.7 months; p = 0.019) (Fig. 2). Conversely, the *H3.3* mutation conferred a poorer outcome in the pediatric DMGs when compared to those with *H3.1* K27M (median OS of 10.1 vs 14.2 months; p < 0.001) (Fig. 3). These results were confirmed by multivariate Cox regression analyses with the only exception in the adult population, which was not statistically significant (*H3.3* vs *H3.1*; HR 0.217; 95% CI 0.017–2.736) (Tables S1, S2).

Table 1 Patient characteristics of *H3.1* and *H3.3* K27M-mutant DMGs

Variables	*H3.1* K27M (n = 102)	*H3.3* K27M (n = 529)	p-value*
Age, median (IQR) (years)	5.0 (4.2–6.9)	11.0 (6.7–21.5)	**< 0.001**
Age group, no. (%)			**< 0.001**
Pediatric	97 (95.1)	383 (72.4)	
Adult	5 (4.9)	146 (27.6)	
Gender, no. (%)			0.130
Female	54 (55.1)	234 (46.8)	
Male	44 (44.9)	266 (53.2)	
Tumor location, no. (%)			**0.001**
Intracranial	100 (99.0)	468 (88.8)	
Spinal cord	1 (1.0)	59 (11.2)	
Chemotherapy, no. (%)			**0.041**
No	10 (25.6)	30 (13.0)	
Yes	29 (74.4)	200 (87.0)	
Radiotherapy, no. (%)			0.990
No	1 (6.3)	13 (7.4)	
Yes	15 (93.8)	162 (92.6)	
Surgery, no. (%)			**0.048**
Biopsy	7 (100)	99 (61.5)	
Resection	0 (0)	62 (38.5)	

IQR interquartile range

*Bold values indicate statistically significant results

Table 2 The prevalence of genetic alterations associated with *H3.1* and *H3.3* K27M mutations

Genetic markers	*H3.1* K27M (%)	*H3.3* K27M (%)	p-value*
ACVR1 mutations	51/78 (65.4)	9/258 (3.5)	**< 0.001**
ATRX loss	0/11 (0)	8/37 (21.6)	0.170
ATRX mutations	1/51 (2.0)	43/257 (16.7)	**0.004**
BRAF mutations	0/41 (0)	7/250 (2.8)	0.599
EGFR amplification	2/5 (40.0)	3/70 (4.3)	**0.033**
FGFR1 mutations	1/16 (6.3)	18/134 (13.4)	0.695
MGMT methylation	0/7 (0)	4/113 (3.5)	1.000
NF1 mutations	2/41 (4.9)	18/185 (9.7)	0.542
PDGFRA amplification	2/37 (5.4)	25/114 (21.9)	**0.022**
PDGFRA mutations	2/31 (6.5)	18/157 (11.5)	0.537
PIK3CA mutations	16/47 (34.0)	23/180 (12.8)	**< 0.001**
PPM1D mutations	3/41 (7.3)	23/160 (14.4)	0.229
TERT mutations	0/11 (0)	7/120 (5.8)	1.000
TP53 mutations	17/65 (26.2)	158/279 (56.6)	**< 0.001**

*Bold values indicate statistically significant results

Stratified by H3K27M genotypes and age groups, patient OS were able to be stratified into different subgroups (Fig. 4). Adult DMGs with *H3.3* had the best OS, followed by pediatric DMGs harboring *H3.1* ($p < 0.001$), and pediatric patients carrying *H3.3* ($p = 0.002$). The survival of adult cases with *H3.1* mutation was only statistically different from *H3.3*-mutant adult DMGs ($p = 0.027$) and were not significantly different from the remaining subgroups, probably because of the very limited number of patients in this subgroup.

Discussion

Infiltrative midline gliomas affecting the brainstem, thalamus, or spinal cord are high-grade tumors with a dismal outcome and are mostly seen in children [8]. Nearly 70–80% of these tumors carry mutations in the histone *H3* gene, which are termed as DMGs and are associated with a worse outcome in comparison with *H3*-wild-type tumors [3–5, 37]. Among DMGs, the *H3.3* K27M mutation is predominant, surprising because only two genes encode H3.3 while the H3.1 protein is encoded by 12 genes [38]. Interestingly, recent evidence indicates that DMG represents a

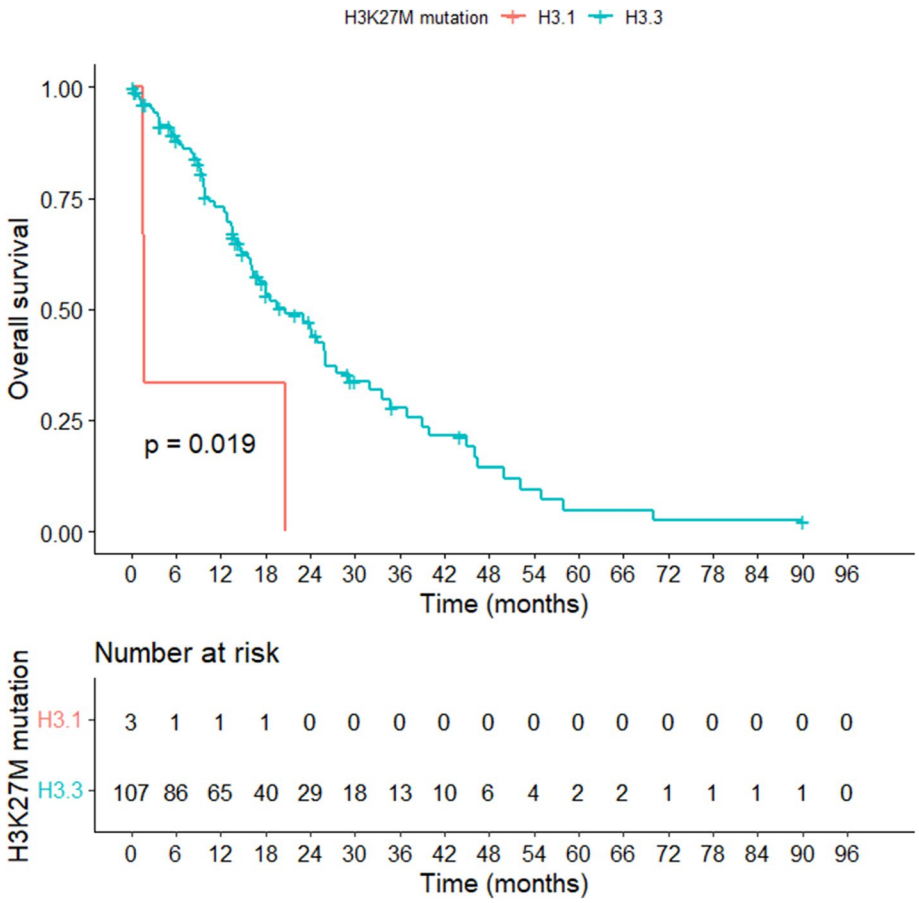

Fig. 2 Kaplan–Meier curve showing the overall survival of adult *H3.1* and *H3.3* K27M-mutant DMGs

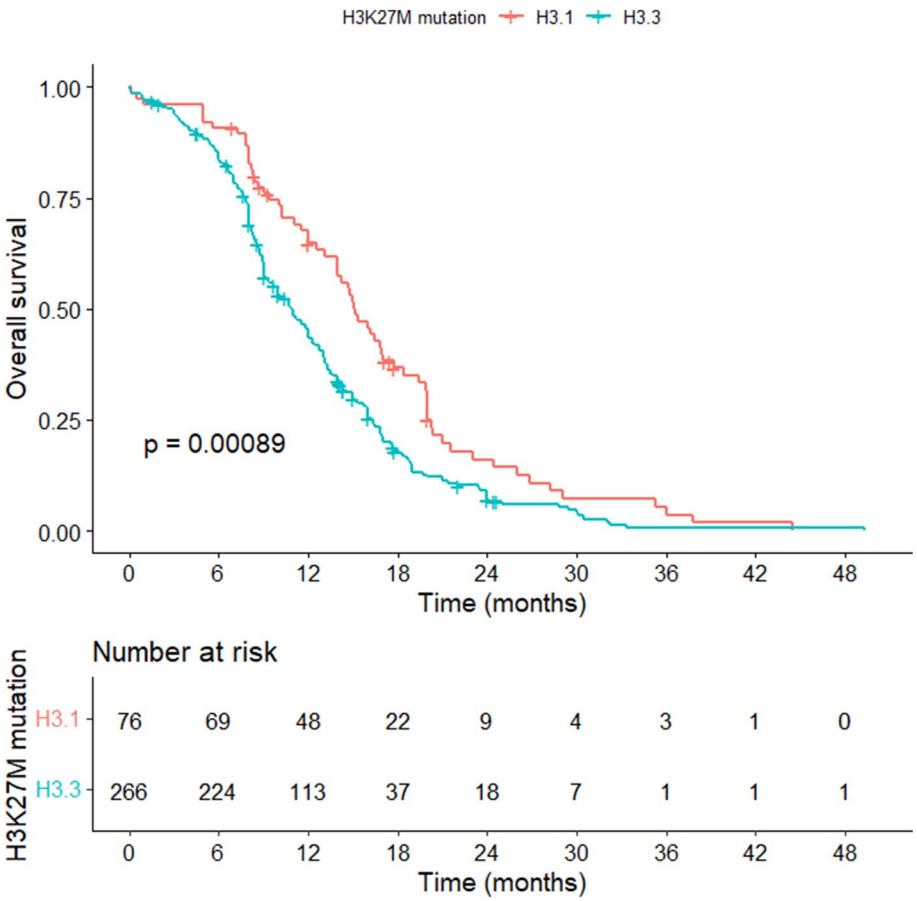

Fig. 3 Kaplan–Meier curve showing the overall survival of pediatric *H3.1* and *H3.3* K27M-mutant DMGs

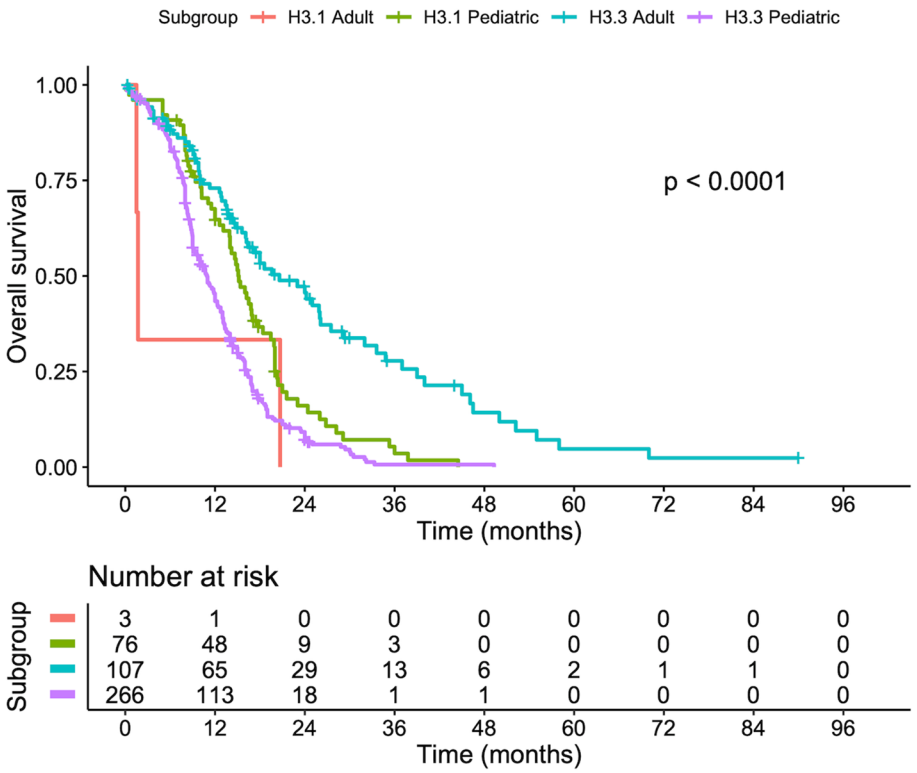

Fig. 4 Kaplan–Meier analysis showing overall survival of different subgroups stratified by H3K27M genotypes and patient age

heterogeneous disease with distinct genetic and molecular profiles in adults in comparison to children [3, 11, 39]. Several studies showed that *H3.1* K27M mutation is more commonly detected in pediatric patients and rarely seen in adults [6, 11, 40, 41]. Additionally, *H3.3* K27M mutation has been reported to affect all anatomical structures of the midline [6, 13, 28] whereas *H3.1*-mutated DMGs were mainly restricted in the brainstem region [11, 13]. Our integrated analyses confirmed these discrepancies between the two *H3* genotypes and revealed the differences in treatment patterns between them. Because *H3.1*-mutant DMGs are primarily located in the pons and thalamus, the rate of tumor resection of these tumors is lower as compared to *H3.3*-mutated DMGs.

Although histone H3.1 and H3.3 proteins are very similar in their amino acid sequences, they are deposited into the chromatin through different pathways and associated with a distinct molecular entity [11]. The H3.1 and H3.2 proteins—also referred to as "canonical" H3—are linked with an earlier onset of gliomagenesis, primarily produced during the DNA synthesis phase of the cell cycle, and deposited throughout the genome [42]. On the other hand, histone H3.3 not only functions as canonical H3 in the nucleosome, but also is expressed throughout the cell cycle and accumulates at sites of histone turnover [43]. It has also been suggested that *H3.1* and *H3.3* K27M-mutant tumors may derive from distinct progenitor cells or at different steps in the differentiation of cell lineage [44]. However, the differences regarding how *H3.1* and *H3.3* K27M mutations involve in the gliomagenesis of DMGs, and how they affect the patient outcomes remained investigational. A multicenter study demonstrated that long-term survivors of diffuse intrinsic pontine glioma are more likely to carry *H3.1* mutation whereas majority of patients with short-term prognosis have *H3.3* mutation [45].

Our results showed that the *H3.1* K27M mutation confers a favorable prognosis as compared to the *H3.3* K27M mutation in pediatric DMGs; however, this was not the case in the adult population. It is still poorly understood as to why these H3K27M mutations have different prognoses in pediatric and adult patients. There are several plausible explanations for a better prognosis of *H3.1* K27M mutation in pediatric patients. First, it has been well established that the cooccurrence of *ACVR1* mutation in H3K27M DMGs is associated with a longer survival [35, 46] and *ACVR1* mutations are only seen in pediatric *H3.1* K27M-mutated DMGs [35, 47, 48] as compared to *H3.3*-mutant tumors. Additionally, DMG patients harboring *H3.1* K27M mutations are more clinically responsive to radiotherapy than those with *H3.3* mutation [11]. Conversely, in the adult population, *H3.3*-mutated tumors were associated with better survival in comparison with *H3.*1-mutated tumors. The mutational differences highlight that these are entities with distinct biological processes. Although we failed to establish a significant association of *H3.3* mutation with prolonged survival in the multivariate model, it should be noted that the result might be skewed by the rarity of the *H3.1* mutation in the adult population.

Our results are of clinical interest as they may provide insights into the survival difference between *H3.1* and *H3.3* K27M mutations and may have therapeutic applications in pediatric and adult populations. Therefore, genotyping of H3K27M mutations in midline gliomas should be routinely recommended for patients in clinical practice. Currently, published guidelines favor the use of immunohistochemistry for the detection of H3K27M mutations in midline gliomas because of its low cost, rapid turnaround time, and easy access [1, 9, 49]. A major drawback of this method is strong immunoreactivity of existing antibodies to both *H3.1* and *H3.3* proteins.

This is the first study to show that the prognostic outcome of H3K27M mutation genotypes is modulated by patient age. However, it has several limitations that need to be discussed. First, we could not avoid selection bias and unmeasured confounders because most included studies were retrospective. Second, our results are likely influenced by the rarity of DMG with H3K27M mutation in adults so the survival differences between *H3.1* and *H3,3* in adults should be interpreted with caution. Hopefully these findings and others inspire multiple centers to pool their data in this rare patient population. Future multicenter studies and/or meta-analyses with additional data for *H3.1*-mutant DMG in adult population are needed to confirm the prognostic differences of *H3.1* – vs *H3.3*-mutant DMGs in adults.

In conclusion, the present study demonstrated that when compared to the *H3.3* variant, the *H3.1* K27M mutation is associated with a favorable prognosis in the pediatric DMGs but might portend an adverse outcome in the adult population. Routine genotyping of H3K27M mutations in DMGs in newly diagnosed DMGs may further refine our understanding and prediction of patient survival.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-022-04027-2.

Acknowledgements Not applicable

Author contributions HGV: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, writing original, review, and editing. TNNM: data curation, formal analysis, investigation, methodology, writing original, review, and editing. HTL: data curation, formal analysis, investigation, methodology, review, and editing. IFD: data curation, formal analysis, investigation, methodology, project administration, validation, review, editing, and supervision. All authors have read and approved the manuscript.

Funding This study receives no funding support.

Data availability Further data inquiries can be directed to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

Consent for publication Not applicable.

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