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Circumscribed/non-diffuse histology confers a better prognosis in H3K27M-mutant gliomas

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Diffuse midline gliomas harboring a recurrent H3 lysine 27-to-methionine (p.Lys27Met, H3K27M) constitute a recently defined pathologic entity with a particularly poor prognosis. They mainly occur in midline structures, such as the pons and thalamus of children and young adults, and are highly infiltrative [2]. More recently, case reports have described the H3K27M mutation in circumscribed (non-diffuse) gliomas, many of which are low-grade (e.g., pilocytic astrocytoma, ganglioglioma) [1, 3–5] (additional references are provided in Online Resource 1). Because of the rarity of these tumors, it is unknown whether they carry the poor clinical outcome ascribed to H3K27M-mutant infiltrating gliomas of the midline. Here, we address this gap in our knowledge by performing an integrated meta-analysis on collated clinical and pathologic data from published studies, data repositories, and collaborative efforts.

A systematic search of the literature was performed from 2012 to November, 2017. Tumors were categorized based on diagnosis, location, histologic grade, growth pattern, and H3K27M mutation status. IDH 1/2-mutant diffuse gliomas were excluded to avoid bias arising from the good prognosis attributed to this mutation. Circumscribed gliomas included pilocytic astrocytoma, ganglioglioma/glioneuronal tumor/ganglion cell tumor, pleomorphic xanthoastrocytoma, and ependymoma. Data from The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov/) was obtained through the cBioPortal and PedcBioPortal for Cancer Genomics. Factors extracted included age, sex, overall survival, tumor location, histopathologic diagnosis and WHO grade. Patient samples were then cross-referenced across studies to filter out duplicate data. Cases were also acquired from our in-house sequencing efforts and through collaboration with the Mayo Clinic in Rochester, Minnesota. Co-occurring mutations were also documented. The endpoint extracted from all data sources was overall survival (OS). Survival functions were estimated using the Kaplan-Meier method and differences analyzed with the Log-rank (Mantel-Cox) test using GraphPad

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Prism software (version 7). The Cox-proportional hazards model was used to calculate hazard ratios (HR) using SPSS (version 24, IBM). All studies were approved by ethics committees at the respective institutions. See Online Resource 1 for further details of the methods.

Among published studies and through institutional collaboration, we identified 28 cases of H3K27M-mutant circumscribed gliomas (grade I: n=19; grade III, n=9). Histopathology included pilocytic astrocytoma (n=7), ganglioglioma (n=10), anaplastic ganglioglioma (n=3), glioneuronal tumor (n=1), anaplastic glioneuronal tumor (n=1), ganglion cell tumor (n=1; Fig. 1a–d), anaplastic ependymoma (n=3), and circumscribed glioma, not further specified (n=2) (see Online Resource 2 for references and case details). Strikingly, more than 96% (n=26/27 cases with location provided) of H3K27M-mutant circumscribed gliomas occurred within the midline, including the brainstem (n=7), thalamus (n=5), cerebellum (n=2), spinal cord (n=8) and other midline regions (peduncle, posterior fossa, midline-not further specified; n=4) (Fig. 1g). Of the remaining two cases, one was reported in the cerebrum, while the location was not specified for the other. H3K27M mutations occurred in *H3F3A* (n=21), *HIST1H3B* (n=1), *HIST1H3C* (n=1), and five cases were detected by immunohistochemistry. Information on co-occurring somatic mutations were available in 50% (14/28) of cases. The most frequent alteration was *BRAF* V600E (n=7) mutations followed by *ATRX* (n=3), *FGFR1* N546K (n=2), and *NF1* (n=2) (see Online Resource 2). Copy number alterations were reported in chromosomes 13 and 17 in two tumors.

Survival information was available for 21 cases (grade I: n=14; grade III: n=7). Univariate analysis of these tumors demonstrated poor OS compared to H3-wildtype circumscribed gliomas (n=59; grade I: n=51; grade III: n=8) (Log rank, $p<0.0001$), but a significantly improved OS compared to H3/IDH-wildtype (Log rank, $p=0.025$) and H3K27M-mutant diffuse gliomas (Log rank, $p<0.0001$) (Fig. 1e). This association remained significant after matching tumors for grade (grade I, Log-rank, $p<0.0001$; Fig. 1f) and treatment (chemotherapy and/or radiotherapy, Log-rank, $p<0.0001$; Supp. Fig. [Online Resource 3]). Cox regression analysis with age, sex, grade, and mutation status included as covariates showed the H3K27M mutation remained an independent predictor of OS (HR, 5.980; 95% CI, 1.839–19.445; $p=0.003$; Fig. 1h).

These results confirm that the poor prognosis of the H3K27M mutation also extends to circumscribed gliomas. While H3K27M-mutant circumscribed gliomas show poor survival compared to H3-wildtype circumscribed gliomas, prognosis remains significantly better than both H3K27M-mutant and H3-wildtype diffuse gliomas. This has important implications regarding the current WHO grading of H3K27M-mutant diffuse gliomas, which are uniformly labeled as grade IV. However, we note that an important limitation to our study is the relatively short follow-up duration, largely owing to the rarity of these tumors. We also show that H3K27M-mutant circumscribed gliomas show a similar predilection for midline regions. Our data suggest that midline circumscribed gliomas should be routinely tested for H3K27M mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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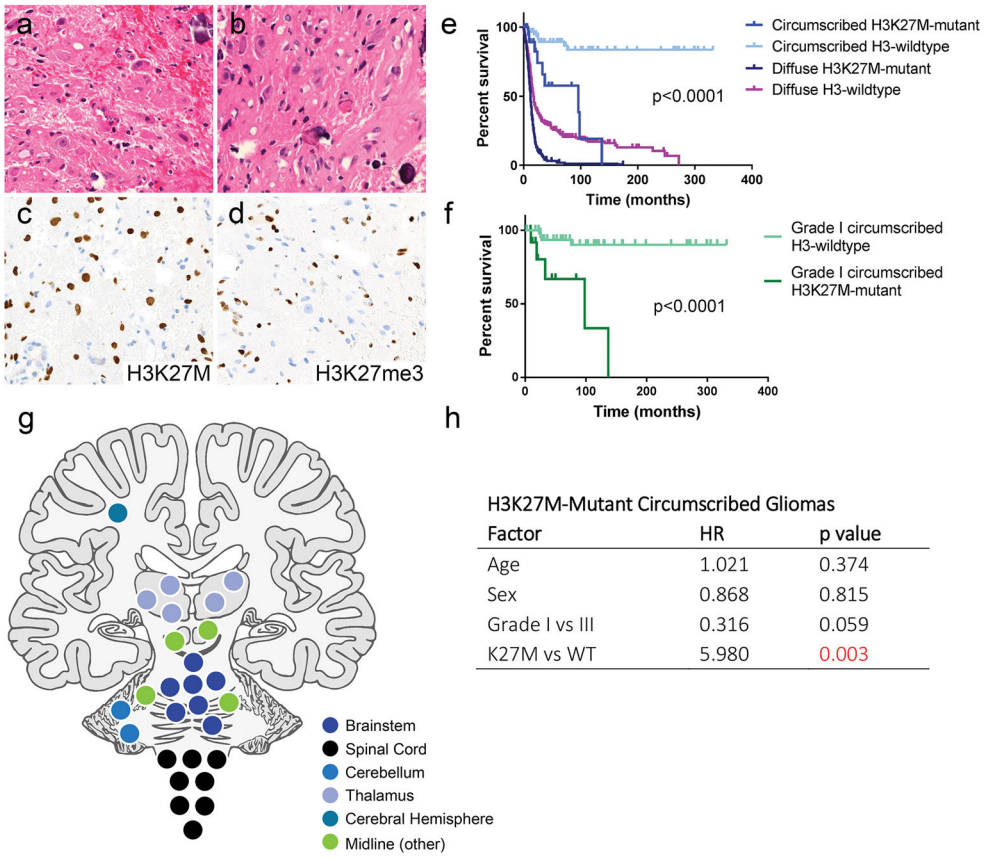
References

1. Kleinschmidt-DeMasters BK, Donson A, Foreman NK, Dorris K. H3 K27M Mutation in Gangliogliomas can be Associated with Poor Prognosis. Brain Pathol. 2017; 27:846–850. DOI: 10.1111/bpa.12455 [PubMed: 28378357]
2. Louis, DN., Ohgaki, H., Wiestler, OD., Cavenee, W. WHO Classification of Tumours of the Central Nervous System. The International Agency for Research on Cancer; City: 2007.
3. Nguyen AT, Colin C, Nanni-Metellus I, Padovani L, Maurage CA, Varlet P, Miquel C, Uro-Coste E, Godfraind C, Lechapt-Zalcman E, et al. Evidence for BRAF V600E and H3F3A K27M double mutations in paediatric glial and glioneuronal tumours. Neuropathol Appl Neurobiol. 2015; 41:403–408. DOI: 10.1111/nan.12196 [PubMed: 25389051]
4. Orillac C, Thomas C, Dastagirzada Y, Hidalgo ET, Golfinos JG, Zagzag D, Wisoff JH, Karajannis MA, Snuderl M. Pilocytic astrocytoma and glioneuronal tumor with histone H3 K27M mutation. Acta Neuropathol Commun. 2016; 4:84.doi: 10.1186/s40478-016-0361-0 [PubMed: 27519587]
5. Pages M, Beccaria K, Boddaert N, Saffroy R, Besnard A, Castel D, Fina F, Barets D, Barret E, Lacroix L, et al. Co-occurrence of histone H3 K27M and BRAF V600E mutations in paediatric midline grade I ganglioglioma. Brain Pathol. 2016; doi: 10.1111/bpa.12473



H3K27M-Mutant Circumscribed Gliomas

Factor	HR	p value
Age	1.021	0.374
Sex	0.868	0.815
Grade I vs III	0.316	0.059
K27M vs WT	5.980	0.003

Fig. 1.

Histopathology, localization, and survival analyses in H3K27M-mutant circumscribed gliomas.

a–d. Representative histology of a ganglion cell tumor (**a–b**, H&E) with nuclear expression of the H3K27M mutant protein (**c**) and concurrent loss of H3K27me3 (**d**)

e. Kaplan-Meier estimation shows stratification of overall survival based on growth pattern and H3K27M mutation status (circumscribed glioma H3-wildtype, n=63; circumscribed glioma H3K27M-mutant, n=21; diffuse glioma H3/IDH-wildtype, n=550; diffuse glioma H3K27M-mutant, n=432).

f. H3K27M mutation demonstrated a worse prognosis compared to H3-wildtype tumors in grade I-matched circumscribed gliomas.

g. Locations of H3K27M-mutant circumscribed gliomas.

h. Cox regression analysis.