ABSTRACT

Nat Genet. 2022 Dec;54(12):1865-1880. doi: 10.1038/s41588-022-01205-w. Epub 2022 Dec 5.

K27M in canonical and noncanonical H3 variants occurs in distinct oligodendroglial cell lineages in brain midline gliomas.

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Canonical (H3.1/H3.2) and noncanonical (H3.3) histone 3 K27M-mutant gliomas have unique spatiotemporal distributions, partner alterations and molecular profiles. The contribution of the cell of origin to these differences has been challenging to uncouple from the oncogenic reprogramming induced by the mutation. Here, we perform an integrated analysis of 116 tumors, including single-cell transcriptome and chromatin accessibility, 3D chromatin architecture and epigenomic profiles, and show that K27M-mutant gliomas faithfully maintain chromatin configuration at developmental genes consistent with anatomically distinct oligodendrocyte precursor cells (OPCs). H3.3K27M thalamic gliomas map to prosomere 2-derived lineages. In turn, H3.1K27M ACVR1-mutant pontine gliomas uniformly mirror early ventral NKX6-1+/SHH-dependent brainstem OPCs, whereas H3.3K27M gliomas frequently resemble dorsal PAX3+/BMP-dependent progenitors. Our data suggest a context-specific vulnerability in H3.1K27M-mutant SHH-dependent ventral OPCs, which rely on acquisition of ACVR1 mutations to drive aberrant BMP signaling required for oncogenesis. The unifying action of K27M mutations is to restrict H3K27me3 at PRC2 landing sites, whereas other epigenetic changes are mainly contingent on the cell of origin chromatin state and cycling rate.

DOI: 10.1038/s41588-022-01205-w
PMCID: PMC9742294
PMID: 36471070 [Indexed for MEDLINE]

Conflict of interest statement: Competing Interests Statement S.P. is a member of the advisory board for Bayer, Novartis and AstraZeneca and has received speaker fees from Bayer and Esai, outside of the submitted work. All other authors declare no competing interests.