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# Characteristics of H3K27M-mutant diffuse gliomas with a non-midline location

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## Abstract

**Purpose:** Diffuse midline gliomas (DMG) with H3K27 alterations (H3K27M-DMG) are a highly aggressive form of brain cancer. In rare cases, H3K27 mutations have been observed in diffuse non-midline gliomas (DNMG). It is currently unclear how these tumors should be classified. Herein, we analyze the characteristics of DNMG with H3K27M mutations.

**Methods:** We reviewed the clinical, radiological and histological characteristics of all patients with an H3K27M mutated diffuse glioma diagnosed in our institution, between 2016 and 2023, to identify cases with a non-midline location. We then performed a molecular characterization (DNA methylation profiling, whole genome and transcriptome sequencing or targeted sequencing) of patients with an H3K27M-mutant DNMG and reviewed previously reported cases.

**Results:** Among 51 patients (18 children and 33 adults) diagnosed with an H3K27M diffuse glioma, we identified two patients (4%) who had a non-midline location. Including our two patients, 39 patients were reported in the literature with an H3K27M-mutant DNMG. Tumors were most frequently located in the temporal lobe (48%), affected adolescents and adults, and were associated with a poor outcome (median overall survival was 10.3 months (0.1-84)). Median age at diagnosis was 19.1 years. Tumors frequently harbored TP53 mutations (74%), ATRX mutations (71%) and PDGFRA mutations or amplifications (44%). In DNA methylation analysis, H3K27M-mutant DNMG clustered within or close to the reference group of H3K27M-mutant DMG. Compared to their midline counterpart, non-midline gliomas with H3K27M mutations seemed more frequently associated with PDGFRA alterations.

**Conclusion:** DNMG with H3K27M mutations share many similarities with their midline counterpart, suggesting that they correspond to a rare anatomical presentation of these tumors. This is of paramount importance, as they may benefit from new therapeutic approaches such as ONC201.

**Keywords:** Diffuse intrinsic pontine glioma; Diffuse midline glioma H3 K27-altered; H3K27M; H3K28M; Methylation; Non-midline; Pediatric glioma.