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Genetic alteration analysis of non-pediatric diffuse midline glioma, H3 K27-altered

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Abstract

Diffuse midline gliomas with H3 K27-alteration (DMGH3) are lethal and inoperable brain tumors. Although DMGH3s mainly occur in pediatric patients, they have also occurred in adult patients. This study aimed to analyze the clinicopathological significance of targetable genetic alterations in non-pediatric DMGH3. Next-generation sequencing (NGS) was conducted on 18 non-pediatric DMGH3 patients to analyze additional genetic alterations. The median age at diagnosis was 35 years, and the mean follow-up duration was 762 days. Fourteen cases involved the thalamus-hypothalamus (77.8%). Histologic high-grade features (WHO histologic grade ≥3) were observed in 11 (61.1%) patients. H3F3A (H3 K27M) alterations were identified in all 18 patients using immunohistochemistry and NGS. TP53 mutations were found in 11 patients (61.1%), FGFR1 or PIK3CA in 3 (16.7%), ATRX in 6 (33.3%), NF1 in 4 (22.2%), and KRAS or ATM in 1 (5.6%). TP53 mutations were significantly correlated with high-grade histological features and worse overall survival (OS) ($P < 0.05$). Despite non-pediatric DMGH3 cases exhibiting superior OS compared to pediatric DMGH3 cases, TP53 mutations were associated with poorer OS outcomes. Notably, FGFR1 and PIK3CA mutations, which have been identified as potential targetable genes, were detected. In conclusion, non-pediatric DMGH3s showed predominant tumor localization within the thalamus and improved prognosis compared to those in pediatric cases, with TP53 alterations correlating with high-grade histology and shorter survival. Genetic profiling, particularly identifying targetable mutations like FGFR1 and PIK3CA, could inform personalized treatment strategies and improve patient outcomes.

Keywords: Brain tumor; Diffuse midline glioma; H3 K27M; Next-generation sequencing; TP53.