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# Pediatric and Adolescent/Young Adult High-Grade Gliomas With Adult-Type Molecular Features

Jyotsna Singh <sup>1</sup>, Supriya Bhardwaj <sup>1</sup>, Swati Singh <sup>1</sup>, Shabnam Mansoori <sup>1</sup>, Srinidhi Vasant <sup>1</sup>, Kirti Srivastava <sup>1</sup>, Shweta Kedia <sup>2</sup>, Ajay Garg <sup>3</sup>, Ashish Suri <sup>2</sup>, Mehar Chand Sharma <sup>1</sup>, Chitra Sarkar <sup>4</sup>, Vaishali Suri <sup>1</sup>

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## Abstract

High-grade gliomas (HGGs) in pediatric and adolescent/young adult (AYA) patients are biologically heterogeneous. Most exhibit pediatric-type molecular features, but a subset shows adult-type DNA methylation profiles with distinct diagnostic and therapeutic implications. We retrospectively analyzed 60 consecutive HGG, NOS cases in patients aged 0-39 years. Genome-wide DNA methylation profiling was performed using two independent brain tumor classifiers, with parallel copy-number analysis, and final diagnoses were reached by integrating epigenetic signatures with histopathology; targeted next-generation sequencing was undertaken in selected tumors. Adult-type molecular profiles were identified in 14 of 60 cases (23.3%), comprising 11 glioblastomas, IDH-wildtype (GBM RTK I, RTK II, and mesenchymal) and 3 adult-type diffuse high-grade gliomas, IDH-wildtype, subtype B, with 35.7% (5/14) occurring in patients  $\leq 18$  years. Recurrent alterations included NF1 (87.5%), PTEN (62.5%), and TERT promoter mutations (25%), with a single BRAF V600E-mutant tumor, while the classical +7/ - 10 signature was infrequent and MGMT promoter methylation was largely absent in GBM, IDH-wildtype. This study demonstrates that a substantial subset of pediatric and AYA HGGs harbor molecularly adult-type signatures, revealing the limitations of conventional histopathology and immunohistochemistry, challenging age-based diagnostic paradigms, and highlights the value of methylation profiling for diagnostic refinement, detection of targetable alterations in younger patients.

**Keywords:** AYA HGGs; DNA methylation profiling; GBM IDH-wildtype; High-grade glioma; MAPK pathway.

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