



Molecular neuropathology: an essential and evolving toolbox for the diagnosis and clinical management of central nervous system tumors

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Abstract

Molecular profiling has transformed the diagnostic workflow of CNS tumors during the last years. The latest WHO classification of CNS tumors (5th edition), published in 2021, pushed forward the integration between histopathological features and molecular hallmarks to achieve reproducible and clinically relevant diagnoses. To address these demands, pathologists have to appropriately deal with multiple molecular assays mainly including DNA methylation profiling and DNA/RNA next generation sequencing. Tumor classification by DNA methylation profiling is now a critical tool for many diagnostic tasks in neuropathology including the assessment of complex cases, to evaluate novel tumor types and to perform tumor subgrouping in heterogeneous entities like medulloblastoma or ependymoma. DNA/RNA NGS allow the detection of multiple molecular alterations including single nucleotide variations, small insertions/deletions (InDel), and gene fusions. These molecular markers can provide key insights for diagnosis, for example, if a tumor-specific mutation is detected, but also for treatment since targeted therapies are progressively entering the clinical practice. In the present review, a brief, but comprehensive overview of these tools will be provided, discussing their technical specifications, diagnostic value, and potential limitations. Moreover, the importance of molecular profiling will be shown in a representative series of CNS neoplasms including both the most frequent tumor types and other selected entities for which molecular characterization plays a critical role.

Keywords Neuropathology · Molecular pathology · DNA methylation profiling · NGS · CNS tumors

Introduction

The evaluation of specific molecular hallmarks has become a mandatory step for diagnosing central nervous system (CNS) tumors since multiple years. Thanks to the publication of the 4th revised edition of the World Health Organization (WHO) classification of CNS tumors in 2016 [1], the concept of an

integrated histopathological and molecular diagnosis has become a cornerstone of oncological neuropathology.

The integrated diagnosis is a diagnosis based on multiple layers which, starting from the conventional histopathological features, is enriched by molecular information. Molecular profiling can help or even provide by itself the diagnostic classification of a tumor type and/or improve the prognostic stratification by complementing histology-based tumor grading and/or help tailor treatment by disclosing potential therapeutic targets. These layers are frequently intertwined and a solid background knowledge about the interpretation of each molecular marker in the relevant diagnostic context is required for their correct translation into diagnostic practice and clinical management.

The latest 2021 WHO classification of CNS tumors (5th edition) [2] has further expanded the significance of molecular profiling in this setting and to date, all the most frequent CNS tumor types envisage the evaluation of a subset of molecular markers in their diagnostic workflow. Additionally, many novel tumor types were

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