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abstract

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abstract

Enhancing Molecular Classifying Accuracy of Pediatric CNS Tumors: A Dual-Classifier Approach Using DNA Methylation Profiling

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Introduction: Accurate classification of pediatric CNS tumors is vital for effective treatment but is limited by traditional histopathology. DNA methylation profiling offers a promising molecular alternative. However, despite its potential clinical value, methylation classifiers remain limited to the research settings. This study evaluates two DNA methylation- based classifiers for CNS tumor diagnosis, aiming for clinical integration, while examining technical factors and the use of visualization and molecular data to resolve diagnostic challenges.

Methodology: We analyzed 96 pediatric pathology tissue samples, including 75 CNS tumors, 10 with CNS non-tumoral lesions and 11 with non-CNS tumors, performing 130 methylation analyses. DNA from both formalin-fixed paraffin-embedded (FFPE) and fresh frozen (FF) tissues were used for methylation profiling using the Illumina Methylation EPIC V1 and V2 arrays. The performance of two DNA methylation-based classifiers (Heidelberg and NIH) was evaluated by comparing the classification results with histopathological diagnoses.

Results: Both classifiers demonstrated an 88% concordance with histopathological diagnoses in CNS tumors. Methylation profiling refined the histological diagnoses in 54.66% of cases and contributed to molecular subtyping in 52% of CNS tumor cases. The analysis in a small percentage of cases (5.33%) exhibited conflicting diagnoses, emphasizing the need for cautious interpretation and re-evaluation of the cases of uncertainty. Interestingly, both classifiers also identified CNS non-tumor tissues from tumor cases, although they misclassified some normal tissues and malformations as CNS tumors.

Conclusion: This study underscores DNA methylation profiling's potential as a complementary tool for classifying pediatric CNS tumors and its path toward clinical use. To the best of our knowledge, this is the first publication comparing two DNA methylation classifiers in a pediatric CNS tumor cohort. The classifiers may improve diagnostic accuracy, particularly in complex cases, but should complement histopathologic methods. Further research is needed to validate their clinical use by refining protocols, addressing limitations, and assessing long-term outcomes. .

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