Medulloblastoma classification

- Robust molecular subgrouping and reference-free aneuploidy detection in medulloblastoma using low-depth whole genome bisulfite sequencing
- Prospective insights into pediatric neurosurgery: transforming care through adverse event analysis
- Integrative Machine Learning Framework for Enhanced Subgroup Classification in Medulloblastoma
- Multifocal medulloblastoma in an adult: a case report and review of the literature
- MRI-based deep learning with clinical and imaging features to differentiate medulloblastoma and ependymoma in children
- Inferred developmental origins of brain tumors from single-cell RNA-sequencing data
- Magnetic resonance imaging (MRI) radiomics in paediatric neuro-oncology: A systematic review of clinical applications, feature interpretation, and biological insights in the characterisation and management of childhood brain tumours
- Automatic smart brain tumor classification and prediction system using deep learning

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In the 5th edition of the WHO classification, medulloblastomas, which are representative pediatric brain tumors, are categorized into four groups: WNT, SHH-TP53 wild, SHH-TP53 mutant, and non-WNT/non-SHH, based on their molecular background. While the histopathological findings still hold importance in predicting prognosis, the histopathological classification is no longer utilized in this edition. SHH medulloblastomas are further subdivided into two groups based on the presence or absence of TP53 mutation, as their clinical characteristics and prognosis differ. Group 3 and Group 4 medulloblastomas, recognized as distinct molecular groups in clinical practice, are combined into a single group called “non-WNT/non-SHH”, because they lack specific molecular pathway activation. Furthermore, based on methylation profiling, dividing SHH medulloblastoma into four subgroups and non-WNT/non-SHH medulloblastoma into eight subgroups was proposed. Understanding the unique clinical characteristics and prognosis associated with each group is crucial. However, it is important to acknowledge that our current understanding of prognosis is based on treatment approaches guided by clinical risk factors such as postoperative residual tumor volume and the presence of metastatic disease. This molecular-based classification holds promise in guiding the development of optimal treatment strategies for patients with medulloblastoma [1)].

Nomenclature

The nomenclature and classification of medulloblastomas are rapidly evolving.

Medulloblastomas, molecularly defined

Medulloblastoma, WNT-activated

Medulloblastoma, SHH-activated and TP53-wildtype

Medulloblastoma, SHH-activated and TP53-mutant

Medulloblastoma non-WNT/non-SSH

In the World Health Organization Classification of Tumors of the Central Nervous System 2021, Group 3 medulloblastoma and group 4 medulloblastomas are grouped together under Medulloblastoma non-WNT/non-SSH, which is in turn divided into 8 subgroups.

Group 3 medulloblastoma

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Group 4 medulloblastoma

Group 4 medulloblastoma.

Misclassification between groups 3 and 4 is common. To address this issue, an AI-based R package called MBMethPred was developed based on DNA methylation and gene expression profiles of 763 medulloblastoma samples to classify subgroups using machine learning and neural network models. The developed prediction models achieved a classification accuracy of over 96% for subgroup classification by using 399 CpGs as prediction biomarkers. We also assessed the prognostic relevance of prediction biomarkers using survival analysis. Furthermore, we identified subgroup-specific drivers of medulloblastoma using functional enrichment analysis, Shapley values, and gene network analysis. In particular, the genes involved in the nervous system development process have the potential to separate medulloblastoma subgroups with 99% accuracy. Notably, our analysis identified 16 genes that were specifically significant for subgroup classification, including EP300, CXCR4, WNT4, ZIC4, MEIS1, SLC8A1, NFASC, ASCL2, KIF5C, SYNGAP1, SEMA4F, ROR1, DPYSL4, ARTN, RTN4RL1, and TLX2. Our findings contribute to enhanced survival outcomes for patients with medulloblastoma. Continued research and validation efforts are needed to further refine and expand the utility of our approach in other cancer types, advancing personalized medicine in pediatric oncology [2)]

Standard-Risk Medulloblastoma

Tumor Resection Rate: Patients with standard-risk medulloblastoma typically have a high rate of tumor resection. This means that during surgery, the neurosurgeon was able to remove a significant portion of the tumor from the brain. Metastasis: Standard-risk patients usually do not have evidence of metastasis, which means that the cancer cells have not spread from the primary tumor site in the cerebellum to other parts of the central nervous system (CNS) or outside the CNS.

High-Risk Medulloblastoma

Tumor Resection Rate: Patients with high-risk medulloblastoma often have a lower rate of tumor

resection. This indicates that during surgery, it may have been challenging to remove the tumor completely, and some cancerous tissue might remain.

Metastasis: High-risk patients typically have evidence of metastasis. This means that the cancer cells have spread from the primary tumor site in the cerebellum to other areas within the CNS or even outside the CNS, such as the spinal cord or other parts of the body. The classification into standard-risk and high-risk categories is essential for treatment planning and prognosis assessment. Patients with standard-risk medulloblastoma may have a more favorable prognosis because of the higher likelihood of complete tumor removal and the absence of metastasis. In contrast, high-risk patients may face a more challenging treatment course and potentially a poorer prognosis due to the presence of metastasis and the difficulty in achieving complete tumor resection.

It's important to note that treatment approaches for these two risk groups may differ, with high-risk patients typically receiving more intensive therapies to address the increased complexity and aggressiveness of their disease. Additionally, advances in molecular and genetic profiling have led to further subclassifications within medulloblastoma, providing a more nuanced understanding of the disease and guiding personalized treatment decisions.

EpiGe-App

EpiGe

The diagnosis of medulloblastoma incorporates the histologic and molecular subclassification of clinical medulloblastoma samples into wingless (WNT)-activated, sonic hedgehog (SHH)-activated, group 3 and group 4 subgroups. Accurate medulloblastoma subclassification has important prognostic and treatment implications.

Harmony alignment reveals novel MB subgroup/subtype-associated subpopulations that recapitulate neurodevelopmental processes, including photoreceptor and glutamatergic neuron-like cells in molecular subgroups GP3 and GP4, and a specific nodule-associated neuronally-differentiated subpopulation in subgroup molecular SHH. Riemondy et al. definitively chart the spectrum of MB immune cell infiltrates, which include subpopulations that recapitulate developmentally-related neuron-pruning and antigen presenting myeloid cells. MB cellular diversity matching human samples is mirrored in subgroup-specific mouse models of MB [3)]

Medulloblastoma, WNT-activated

Medulloblastoma, WNT-activated

Sonic hedgehog medulloblastoma

Sonic hedgehog medulloblastoma.

Medulloblastoma, SHH-activated

Medulloblastoma, SHH-activated

Medulloblastoma, non-WNT/non-SSH

Medulloblastoma non-WNT/non-SSH

Histology

Medulloblastoma histologically defined:

Classic medulloblastoma

Desmoplastic nodular medulloblastoma

Medulloblastoma with extensive nodularity

Medulloblastoma, large cell/anaplastic

Medulloblastoma, NOS.

Localization

see Cerebellar medulloblastomas

see Cerebellopontine angle medulloblastoma

see Multifocal medulloblastoma.

Subgrouping

Immunohistochemistry (IHC)-based and nanoString-based subgrouping methodologies have been independently described as options for medulloblastoma subgrouping, however, they have not previously been directly compared. D'Arcy described the experience with nanoString-based subgrouping in a clinical setting and compare this with our IHC-based results. Study materials included FFPE tissue from 160 medulloblastomas. Clinical data and tumor histology were reviewed. Immunohistochemical-based subgrouping using β-catenin, filamin A and p53 antibodies and nanoString-based gene expression profiling was performed. The sensitivity and specificity of IHC-based subgrouping of WNT and SHH-activated medulloblastomas was 91.5% and 99.54%, respectively. Filamin A immunopositivity highly correlated with SHH/WNT-activated subgroups (sensitivity 100%, specificity 92.7%, $p < 0.001$). Nuclear β-catenin immunopositivity had a sensitivity of 76.2% and specificity of 99.23% for the detection of WNT-activated tumors. Approximately 23.8%

of WNT cases would have been missed using an IHC-based subgrouping method alone. nanoString could confidently predict medulloblastoma subgroup in 93% of cases and could distinguish group 3/4 subgroups in 96.3% of cases. nanoString-based subgrouping allows for a more prognostically useful classification of clinical medulloblastoma samples [4].

Molecular subgrouping was performed by immunohistochemistry (IHC) for beta catenin, GAB1 and YAP1; FISH for MYC amplification, and sequencing for CTNNB1, and by NanoString Assay on the same set of MBs. A subset of cases was subjected to 850k DNA methylation array.

IHC + FISH classified MBs into 15.8% WNT, 16.8% SHH, and 67.4% non-WNT/non-SHH subgroups; with MYC amplification identified in 20.3% cases of non-WNT/non-SHH. NanoString successfully classified 91.6% MBs into 25.3% WNT, 17.2% SHH, 23% Group 3 and 34.5% Group 4. However, NanoString assay failure was seen in eight cases, all of which were > 8-years-old formalin-fixed paraffin-embedded tissue blocks. Concordant subgroup assignment was noted in 88.5% cases, while subgroup switching was seen in 11.5% cases. Both methods showed prognostic correlation. Methylation profiling performed on discordant cases revealed 1 out of 4 extra WNT identified by NanoString to be WNT, others aligned with IHC subgroups; extra SHH by NanoString turned out to be SHH by methylation.

Both IHC supplemented by FISH and NanoString are robust methods for molecular subgrouping, albeit with few disadvantages. IHC cannot differentiate between Groups 3 and 4, while NanoString cannot classify older-archived tumors, and is not available at most centres. Thus, both the methods complement each other and can be used in concert for high confidence allotment of molecular subgroups in clinical practice [5].

The maturation of medulloblastoma into a ganglion cell-rich lesion is very rare, with few well-characterized previous reports. Given the rare nature of this entity, it would be of great value to understand the process of posttreatment maturation and the genetic and treatment factors which contribute to this phenomenon [6].

Pediatric Medulloblastoma

Pediatric Medulloblastoma.

Test and Answers

In the 5th edition of the WHO classification, how are medulloblastomas categorized based on their molecular background? a) Low-risk and high-risk b) Classic and desmoplastic nodular c) WNT, SHH-TP53 wild, SHH-TP53 mutant, and non-WNT/non-SHH d) Standard-risk and high-risk

Which subgroup of medulloblastoma is characterized by activation of the WNT pathway? a) Group 3 b) SHH-activated c) WNT-activated d) Non-WNT/non-SHH

What is the significance of TP53 mutation in SHH medulloblastomas? a) It indicates a better prognosis

b) It indicates a worse prognosis c) It has no impact on prognosis d) It classifies the tumor as a WNT-activated subtype

How many subgroups are non-WNT/non-SHH medulloblastomas divided into based on methylation profiling in the 5th edition of the WHO classification? a) 2 b) 4 c) 6 d) 8

What are the clinical risk factors often used for prognosis assessment in medulloblastoma? a) Molecular subgroups b) Histopathological findings c) Age and gender d) Tumor location and size

Which of the following statements is true regarding the classification of medulloblastoma? a) Histopathological classification is the primary method used in the 5th edition of the WHO classification. b) Molecular subgroups are not considered relevant for treatment planning. c) Molecular subgroups guide the development of optimal treatment strategies. d) All medulloblastomas are classified into two main subgroups: WNT and SHH-activated.

What is the main difference between standard-risk and high-risk medulloblastoma? a) The presence of TP53 mutation b) The rate of tumor resection c) The age of the patient d) The presence of metastasis

Which of the following is NOT a method used for molecular subgrouping of medulloblastoma? a) Immunohistochemistry (IHC) b) NanoString Assay c) FISH for MYC amplification d) DNA methylation analysis

What is the advantage of using NanoString Assay for molecular subgrouping of medulloblastoma? a) It can classify older-archived tumor samples. b) It has a higher success rate in classifying tumors. c) It is based on DNA methylation profiling. d) It cannot be used in clinical practice.

Which subgroup of medulloblastoma is characterized by MYC amplification in some cases? a) WNT-activated b) SHH-activated c) Group 3 d) Group 4

Answers:

c) WNT, SHH-TP53 wild, SHH-TP53 mutant, and non-WNT/non-SHH c) WNT-activated b) It indicates a worse prognosis d) 8 c) Age and gender c) Molecular subgroups guide the development of optimal treatment strategies. b) The rate of tumor resection d) DNA methylation analysis a) It can classify older-archived tumor samples. c) Group 3

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