Molecular Biology Reports
https://doi.org/10.1007/s11033-020-05971-w

MINI REVIEW ARTICLE

Medulloblastoma: "Onset of the molecular era"

Pavan Kumar Dhanyamraju[1] · Trupti N. Patel[2] · Sinisa Dovat[1]

Received: 12 July 2020 / Accepted: 2 November 2020

Abstract
Among brain tumors, Medulloblastoma (MB) is one of the most common, malignant, pediatric tumors of the cerebellum. It accounts for ~20% of all childhood central nervous system (CNS) tumors. Despite, tremendous advances in drug development processes, as well as novel drugs for MB the morbidity and mortality rates, remain high. Craniospinal radiation, high-dose chemotherapy, and surgical resection are the primary therapeutic strategies. Tremendous progress in the field of "genomics" with vast amounts of data has led to the identification of four distinct molecular subgroups in medulloblastoma: WNT group, SHH group, group-III, and group-IV. The identification of these subgroups has led to individualized treatment strategies for each subgroup. Here, we discuss the various molecular subgroups of medulloblastoma as well as the differences between them. We also highlight the latest treatment strategies available for medulloblastoma.

Keywords Medulloblastoma · Molecular subgroups · Therapeutics

Abbreviations

ATO	Arsenic trioxide
BBB	Blood-brain barrier
BRDi	Bromo-domain inhibitors
CNS	Central nervous system
CSF	Cerebrospinal fluid
EGL	External granule layer
GCP	Granule cell precursors
HDACi	Histone deacetylase inhibitors
MB	Medulloblastoma
MBEN	Medulloblastoma with extensive nodularity
MRI	Magnetic resonance imaging
PI3Ki	Phosphatidylinositol 3-kinase inhibitors
SHH	Sonic hedgehog
WHO	World health organization
WNT	Wingless

Introduction

The term "Medulloblastoma" (MB) was first coined by Percival Bailey and Harvey Cushing in the year 1925 [1]. It can be described as a highly invasive pediatric tumor arising from the cerebellum and accounts for ~20% of all childhood central nervous system (CNS) tumors [2]. It is very uncommon in adult patients (post-pubertal) and accounts for ~1% of CNS tumors in this age category [3, 4]. Due to the high morbidity and mortality rates of MB, prompt treatment is of high importance [5]. The genetics of MB differs across various age classes resulting in marked prognostic characteristics that can impact treatment decisions [4]. MB patients display a range of symptoms which include hearing loss, lethargy, facial weakness, cranial nerve defects, vomitings, ataxia, headaches, head tilt, and Parinaud's syndrome (upward gaze and pupillary defect) among others [6]. Multiple treatment strategies consisting of cytotoxic drugs and non-specific approaches introduced in the early 1980s are still used. The major disadvantages of these approaches are severe side effects and long-term disabilities. MB was previously categorized into (1) Classical MB and four different sub-groups, based on the histological features: (2) Desmoplastic or nodular (D/N); (3) Medulloblastoma with extensive nodularity (MBEN); (4) Anaplastic medulloblastoma, and (5) Large-cell variant [5, 6]. But, with advances in genomics MB has been reclassified by the world health organization (WHO) based on molecular profiling into four

✉ Pavan Kumar Dhanyamraju
pdhanyamraju@pennstatehealth.psu.edu

[1] Department of Pediatrics, Pennsylvania State University College of Medicine, Hershey, PA 17033, USA

[2] Department of Integrative Biology, Vellore Institute of Technology, Vellore, India

Published online: 06 November 2020

subtypes: (1) WNT, (2) SHH, (3) Group-III, and (4) Group IV. All these subtypes have distinct molecular and clinical traits [7, 8].

WNT group

The WNT group of MB is the least common and accounts for ~10% of all MB cases [5]. Generally, this group of MBs manifests after 3 years of age [9]. But it has also been observed in post-pubertal and adult patients [4, 10–12]. It affects both genders (males/females) equally [9]. The primary origin of WNT MB is considered as lower rhombic lip progenitor cells [13]. Nearly, 85–90% of WNT-MBs exhibit somatic mutations in *CTNNB1* gene that encodes β-catenin [7, 11, 12]. Such kinds of mutations result in constitutive activation of WNT signaling pathway that occurs through the stabilization of β-catenin. Nuclear accumulation of stabilized β-catenin acts as a co-activator for various transcription factors including the TCF-LEF family, leading to activation of WNT-responsive genes [14]. The other commonly observed feature of this group is monosomy 6 that occurs along with *CTNNB1* mutations [5]. In patients lacking somatic mutations in *CTNNB1* gene, otherwise harbor mutations in *APC*, which is a tumor suppressor gene. *APC* belongs to a complex consisting of CSNK1A, GSK3β, axin1, and axin2 that facilitates phosphorylation-dependent ubiquitylation and β-catenin degradation, explaining the constitutively triggered WNT signaling found in MB patients and *APC* loss-of-function mutations [15]. Furthermore, based on DNA methylation analysis and gene expression data, scientists have divided the WNT group into two subtypes: WNTα and WNTβ [14, 15]. Although both these subgroups exhibit similar survival rates, the main difference being WNTα subtype is observed in children with high monosomy 6 frequency whereas WNTβ subtype is largely seen in adults and older children with low monosomy 6 frequency [14, 15]. *SMARCA4, TP53, DDX3X, CSNK2B, EPHA7,* and *PIK3CA* are some of the other frequently mutated genes in WNT MB [16–19]. The most common type of histology seen in this subtype is classic and LCA [18]. Among the four MB subtypes, the WNT subtype has the highest patient survival (>90%) and the best prognosis [9] but the outcomes in adult WNT-MB patients is not as favorable as that of patients below the age of 16 years [4, 10–12] (Fig. 1).

SHH group

The SHH group of MB accounts for ~30% of all MBs [5]. It is mostly seen in adults (>16 years old) and children (<3 years old) [5]. Both genders are equally affected in this subgroup [20]. The characteristic location of SHH MBs is the cerebellar hemispheres. Granule cell precursors (GCP) of the external granule layer (EGL) are the cells of origin of SHH MBs [8, 10]. The most common histological features of this subgroup are ND, LCA, and Classical [13]. The name SHH comes from the constitutive activation of the sonic hedgehog (SHH) signaling pathway in this subgroup of MBs. Amplification of *GLI-1/2*, mutations in SMO leading to gain of function, and perturbations in SUFU, PTCH1/2 which leads to loss of function are primary causes for SHH driven MBs [21]. Hyperactivation of SHH pathway is considered to be the

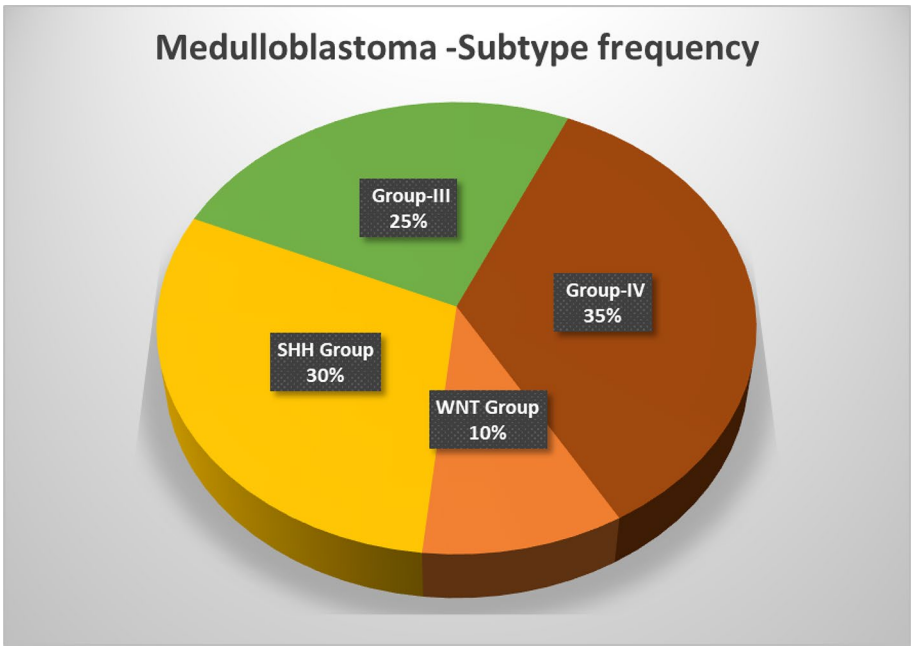

Fig. 1 Graphical representation of molecular subgroups of medulloblastoma: Four different subgroups of medulloblastoma showing their frequency. This figure is based on the data from the specified reference [19]

principal reason for tumorigenesis in patients with SUFU germline mutations and are at a higher risk of developing MB in infancy [22]. Mutations in the PI3K pathway and p53 components have also been reported in SHH MB. Deregulated p53 signaling contributes to defective cell cycle, DNA repair, and apoptosis while mutations in PI3K (receptor tyrosine kinase) signaling promotes cell proliferation, survival, and growth [22]. Further, based on gene expression datasets and DNA methylation pattern SHH-MB has been categorized into four subgroups: SHHα, SHHβ, SHHγ, and SHHδ [23]. The SHHα subgroup is usually observed in children with *GLI2/MYCN* amplification and TP53 mutations. While, both SHHβ and SHHγ manifest in young children. Whereas, SHHδ tumors are noticed in adults harboring mutations in TERT promoter [20]. It has been also demonstrated that adult MB patients harbor more mutational burden than that of childhood MB patients and exhibit 80% of mutations in SMO or PTCH1 [4, 24–26]. In general, SHH MBs have an intermediate prognosis but variations within this subtype have been noticed [20]. For example, the survival rate of SHHβ-MB patients is worse than that of SHHγ-MB patients because of high frequency of metastases. Also, SHH MBs with TP53 mutations show a very poor prognosis [27] (Fig. 2).

Group-III

Group-III MBs accounts for ~25% of all MBs. Males are affected more than females [28]. Classic and LCA are the common histological variants of this group [9]. The cellular origin of this subgroup is neural stem cells [28]. The 5-year overall survival (OS) range of this group is ~39–58% [29]. In children, this is ~58% whereas in nonirradiated infants it is ~45% [25, 30, 31]. Contrary to WNT and SHH MBs where clear evidence of aberrant activation of molecular pathways has been demonstrated but for this group, the elemental cause has not been established yet [30]. The most common mutations observed in this subtype are overexpression of *SMARCA4* and *GABRA5* [32]. Amplification of the proto-oncogene *MYC* has also been observed [32]. Cytogenetic anomalies include isochromosome 17q, gain of chromosomes 18,7,1q as well as the loss of chromosomes 16q,10q, and 8 [33]. Recently, a study based on DNA methylation pattern and integrated gene expression analysis led to the identification of three subtypes in this group. Namely, group 3α,3β, and 3γ [23]. Group 3α tumors are in general observed in young children whereas Group3β, and 3γ are seen in older children [20]. Prognostically group 3α and 3β are more favorable than 3γ [32]. In group 3α loss of chromosome 8q is very frequent and gain of 8q in group 3γ. Loss

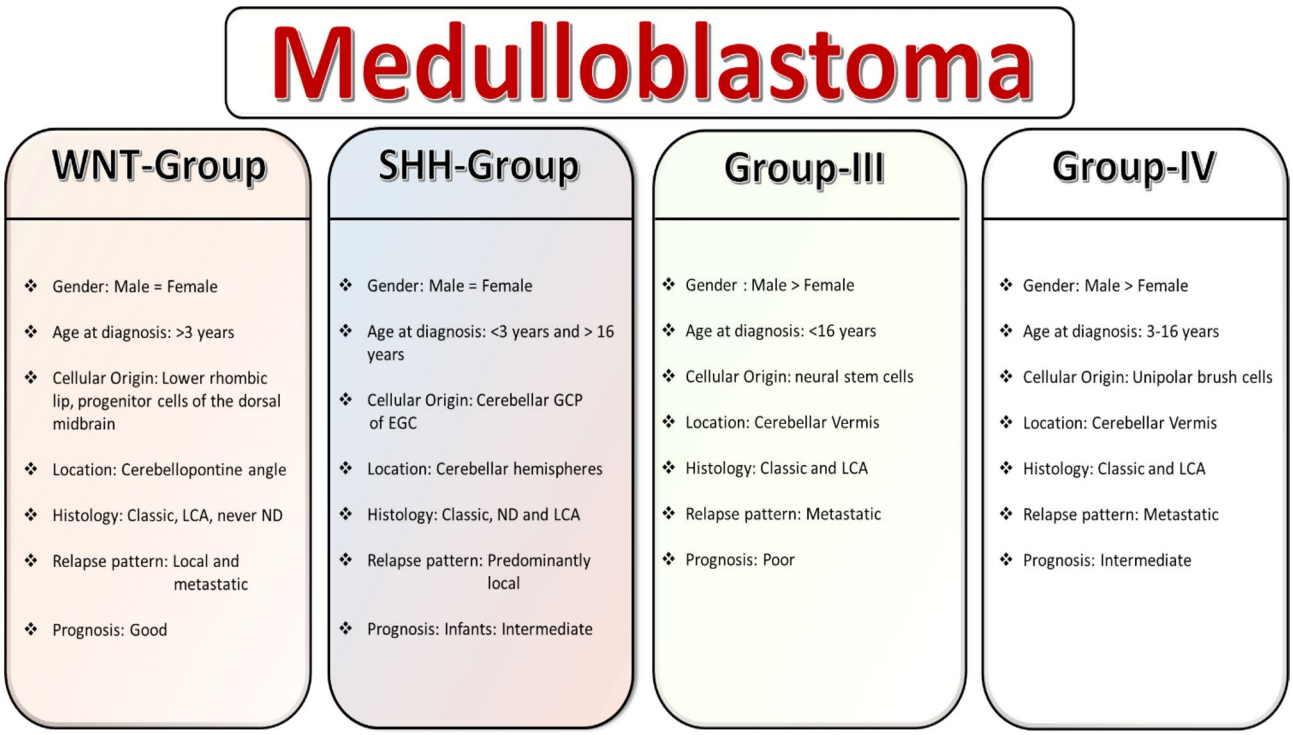

Fig. 2 Graphical representation of various medulloblastoma subgroups. Four different subgroups of medulloblastoma showing gender, age at diagnosis, cellular origin, location, histology, relapse pattern, and prognosis are illustrated. This figure is based on the data from the specified references [9, 19, 27]

of *DDX31*, overexpression of *GFI1/GFI1B* as well as gain of *OTX2* are also frequent in Group 3β [23]. One of the principal reasons for poor prognosis in this group can be attributed to metastases in 50% of the patients at the time of diagnosis [27, 28].

Group-IV

Among the four medulloblastoma subgroups, group-IV is the most common with a frequency of ~35% [9]. The incidence rate of this subtype is more prevalent in males than in females [28]. Classic and LCA are the common histological features of this subgroup [28]. The cellular origin of this group of MBs is unipolar brush cells [28]. A unique signature has not yet been identified for this group via transcriptional profiling. However, *KBTBD4* (6%), *ZMYM3* (6%), *KDM6A* (9%), and *KMT2C* (6%) somatic mutations, overexpression of *GFI1/GFI1B* (5–10%), and *PRDM6* (17%) as well as amplification of *CDK6* (6%), *MYCN* (6%), and *OTX2* (6%) are common [33]. Furthermore, loss of 11p, 8p, 8q, and X and gain of chromosomes 18q and 7 have been observed [9, 11]. Also, the most common aberration observed in this subgroup is isochromosome 17q (80%) [20]. Lately, three different subtypes in Group-IV MBs have been identified namely Group IV-α, Group IV-β, and Group IV-γ [34]. The overall rate of survival and frequency of metastasis at diagnosis among these groups is statistically not significant [20]. Molecularly these three subgroups exhibit differences including *CDK6* and *MYCN* amplification in Group IV-α, duplication of Synuclein Alpha Interacting Protein (SNCAIP) in Group IV-β, and amplification of *CDK6* in Group IV-γ [21, 30].

Treatments

For MB patients the standard treatment options include surgical intervention with maximal tumor resection followed by radiotherapy (RT), and/or chemotherapy (CT) [20, 32, 35]. Treatment with RT consists of a standard dose of 23.4 Gray (Gy) for low-risk individuals whereas for high-risk individuals it ranges between 36 and 39 Gy [20]. Post radiation MB patients are treated with chemotherapeutic agents like cisplatin, etoposide, methotrexate, cyclophosphamide, and lomustine [36]. For children below the age of 3 years, autologous stem cell transplantation and CT consisting of multiple drugs are considered to circumvent the long-term side effects of RT [37, 38]. Further, the therapeutic options vary subject to risk factors associated with a patient's health [32, 35]. Due to the location of MB tumors, early detection is difficult and tumor metastasis is often observed in 30% of patients at the time of diagnosis [5]. Improved diagnostics like liquid biopsy methods and serum markers for early detection of MBs have been researched and are currently under preclinical evaluation [4, 39]. Additionally, cerebrospinal fluid (CSF) from MB patients as well as circulating tumor cells in the blood offer a novel method to detect MB in early stages [4, 39]. It has been demonstrated that ~25% of MB patients suffer from a multitude of side effects ranging from dysarthria, hearing loss, pituitary hormone deficiency, short stature, stroke, cavernous malformations, cataracts, cerebrovascular disease, intracranial hemorrhage, endocrine disorders, neurocognitive deficits, as well as secondary tumors which can be attributed to non-specific chemotherapy, craniospinal radiotherapy, and surgery [8, 40] therefore new treatment modalities are imperative for MB patients to decrease the side effects [20].

In general, the treatment strategies for adult MBs are similar to that of pediatric MBs due to the assumption that in both the populations the tumors behave alike [4]. Also, the OS rates between adult MBs and that of pediatric MB are very similar [4]. However, certain differences between adult MBs and pediatric MBs have been noticed, late recurrences, desmoplastic histology, and lateral cerebellar locations are particularly observed in adult MBs. Furthermore, the prognostic factors that are well understood in childhood MBs patients have not been very well characterized in adult MBs patients. Due to the rarity of MB in adults, most of the data is based on retrospective studies, prospective studies are encouraged to determine as well as to establish prognostic factors in adult MB patients [41]. The advances in MB genomics and the identification of various molecular subgroups of MB has opened new avenues for personalized targeted therapy for MB patients. Several clinical trials are presently underway that hold promise as an effective therapeutic strategy for individual molecular subgroups of MB. For example, it has been shown that the blood-brain barrier (BBB) which plays a crucial role in maintaining the tumor microenvironment (TME) prevents cancer cells from directly getting exposed to the chemotherapeutic drugs present in the bloodstream [20]. WNT MBs, however, have been reported as having a lack of functional BBB relative to other MB subgroups, rendering this subset of tumors potentially more vulnerable to chemotherapeutic drugs that cannot cross the BBB [20, 42]. For WNT group, clinical trials particularly focussed on CT and RT are given importance than targeting the WNT pathway itself as tumors in this subtype are permeable to BBB due to dysfunctional WNT pathway enabling greater penetration of chemotherapeutic drugs into cancer cells [20, 30, 42]. Additionally, multiple clinical trials with low doses of CT and RT are currently in progress (NCT02212574, NCT02066220, and NCT02724579) [20]. Histone deacetylase inhibitors (HDACi) involved in the disruption of chromatin remodeling are also suggested in treating WNT MBs [24].

With regard to SHH MB group, several therapeutic strategies have been developed and many more are under investigation. Due to the diverse mutational landscape observed in SHH MB patients, no one particular drug is effective in treating this group of MBs. Hence, high throughput studies are being undertaken to understand and characterize the tumor sample/s at various molecular levels (NCT02417324 and NCT02238899) for precision-based medicine [4]. SHH MB patients with mutations in SMO and PTCH1 are treated with vismodegib [20, 43, 44] but high-risk SHH MB patients with *GLI2* and *MYCN* amplifications as well as mutations in *SUFU* cannot benefit from vismodegib [26, 31, 45, 46]. Therefore, alternative treatment strategies are required in such cases [26, 31, 45, 46]. Alternative therapeutic strategies such as proton therapy and tomotherapy are also being explored [4]. In clinical trial-NCT01857453 reduced RT dose along with CT was being tested in adult MB patients with intermediate-risk [4]. Combination therapy consisting of temozolomide with sonidegib or temozolomide with ribociclib is given to recurrent and refractory SHH MB patients [4, 20, 43, 47]. Furthermore, fimepinostat, a dual PI3K, and HDAC inhibitor have also been tested in recurrent SHH MB patients (NCT03893487) [20]. Besides this, oral combination therapy consisting of trofosfamide and etoposide has also shown promise. Chemotherapeutic agents like carboplatin (NCT00749723) [4], arsenic trioxide (ATO), bromodomain inhibitors (BRDi) [48], and anti-angiogenesis therapy are also under consideration [48]. In one of the research studies, HDAC6 has been demonstrated to be a potential target for treating SHH MBs [49]. Other ongoing clinical trials include CX4945, a potent CK2 inhibitor which is being tested in recurrent SHH MBs (NCT03904862) [20].

The distinguishing feature of group-III MBs is the amplification of *MYC* proto-oncogene. In a study with murine models, overexpression of *MYC* and inactivation of *TRP53* led to the identification of the crucial role of PI3K/mTOR pathway in group-III MBs [50, 51]. Screening of drugs in this model led to the identification of HDACi like LBH-589 showing synergy with phosphatidylinositol 3-kinase inhibitors (PI3Ki). In another animal study palbociclib, a CDK inhibitor was shown to be active against tumor cells [52]. Bromo-domain inhibitors (BRDi) indirectly targeting *MYC* activity have also been found useful in treating group-III MBs [53]. In a multicentral ongoing clinical trial (NCT01878617) group-III and group-IV MB patients are being treated with gemcitabine and pemetrexed [20, 25]. In clinical trials (NCT04023669 and NCT02255461) checkpoint inhibitors like *CDK1/2/4* and *6* in combination with CT drugs or alone are being tested in refractory and recurrent group-III as well as group-IV MBs [20]. Collectively, several ongoing clinical trials addressing various aspects of MB treatment are under investigation, and search for new targets and therapeutics is in great demand.

Conclusion and future perspective

Medulloblastoma is one of the most common and devastating pediatric central nervous system cancers. Previously, MB was categorized based upon histopathological features. But, due to recent advancements in cancer genomics, scientists have identified various subtypes of MB (WNT, SHH, Group-III, and Group-IV) based on molecular profiling of the tumors [20]. Standard treatment strategies were widely employed for almost all MB patients but now due to the identification of these molecular subtypes, an effective and more precise treatment regimen is possible. Moreover, with the molecular categorization of MB low and high-risk patients can be identified and treated accordingly. Despite these advancements, the side effects of current therapies are of major concern. Therefore, future treatment strategies should be particularly based upon identification of MB subtype upon diagnosis and tailor-made treatment strategy for individual patients based upon the type of mutation they carry. NCT01878617 and NCT02066220 are two clinical trials where the molecular classification of MB is being used and are currently recruiting. Diffusion tensor imaging and the latest magnetic resonance imaging (MRI) techniques are being utilized for visualizing tumors and very convenient in differentiating MB subtypes [4, 54–56]. Furthermore, a better understanding of the signaling pathways, mechanisms involved in MB progression, early diagnosis, and novel therapeutics is the way to move forward.

Author Contributions Conceptualization, manuscript original draft writing, editing PK, manuscript review T.P, S.D. All the authors have read and agreed to the published version of the manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Bailey P, Cushing H (1925) Medulloblastoma cerebelli: a common type of midcerebellar glioma of childhood. Arch Neurol Psychiatr 14:192. https://doi.org/10.1001/archneurpsyc.1925.02200140055002
2. Bahmad HF, Poppiti RJ (2020) Medulloblastoma cancer stem cells: molecular signatures and therapeutic targets. J Clin Pathol 73:243–249. https://doi.org/10.1136/jclinpath-2019-206246
3. Smoll NR (2012) Relative survival of childhood and adult medulloblastomas and primitive neuroectodermal tumors (PNETs). Cancer 118:1313–1322. https://doi.org/10.1002/cncr.26387
4. Franceschi E, Hofer S, Brandes AA et al (2019) EANO–EURACAN clinical practice guideline for diagnosis, treatment, and

follow-up of post-pubertal and adult patients with medulloblastoma. Lancet Oncol 20:e715–e728. https://doi.org/10.1016/S1470-2045(19)30669-2
5. Millard NE, De Braganca KC (2016) Medulloblastoma. J Child Neurol. https://doi.org/10.1177/0883073815600866
6. Huang SY, Yang JY (2015) Targeting the hedgehog pathway in pediatric medulloblastoma. Cancers (Basel) 7:2110–2123
7. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A, Aldape K, Brat D, Collins VP, Eberhart C, Figarella-Branger D, Fuller GN, Giangaspero F, Giannini C, Hawkins C, Kleihues P, Korshunov A, Kros JM, Beatriz Lopes M, Ng HK, Ohgaki H, Paulus W, Pietsch T, Rosenblum M, Rushing E, Soylemezoglu F, Wiestler O, Wesseling P, International Society Of Neuropathology—Haarlem (2014) International Society Of Neuropathology—Haarlem consensus guidelines for nervous system tumor classification and grading. Brain pathol 24(5):429–435. https://doi.org/10.1111/bpa.12171
8. Wang J, Garancher A, Ramaswamy V, Wechsler-Reya RJ (2018) Medulloblastoma: from molecular subgroups to molecular targeted therapies. Annu Rev Neurosci 41:207–232. https://doi.org/10.1146/annurev-neuro-070815-013838
9. Taylor MD, Northcott PA, Korshunov A et al (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123:465–472. https://doi.org/10.1007/s00401-011-0922-z
10. Remke M, Hielscher T, Northcott PA et al (2011) Adult medulloblastoma comprises three major molecular variants. J Clin Oncol 29:2717–2723. https://doi.org/10.1200/JCO.2011.34.9373
11. Kool M, Korshunov A, Pfister SM (2012) Update on molecular and genetic alterations in adult medulloblastoma. Memo – Mag Eur Med Oncol 5:228–232. https://doi.org/10.1007/s12254-012-0037-9
12. Goschzik T, Schwalbe EC, Hicks D et al (2018) Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial. Lancet Oncol 19:1602–1616. https://doi.org/10.1016/S1470-2045(18)30532-1
13. Kijima N, Kanemura Y (2016) Molecular classification of medulloblastoma. Neurol Med Chir (Tokyo) 56:687–697. https://doi.org/10.2176/nmc.ra.2016-0016
14. Thompson MC, Fuller C, Hogg TL et al (2006) Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol 24:1924–1931. https://doi.org/10.1200/JCO.2005.04.4974
15. Waszak SM, Northcott PA, Buchhalter I et al (2018) Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol 19:785–798. https://doi.org/10.1016/S1470-2045(18)30242-0
16. Zhao F, Ohgaki H, Xu L et al (2016) Molecular subgroups of adult medulloblastoma: a long-term single-institution study. Neuro-Oncology 18:982–990. https://doi.org/10.1093/neuonc/now050
17. Robinson G, Parker M, Kranenburg TA et al (2012) Novel mutations target distinct subgroups of medulloblastoma. Nature 488:43–48. https://doi.org/10.1038/nature11213
18. Northcott PA, Korshunov A, Witt H et al (2011) Medulloblastoma comprises four distinct molecular variants. J Clin Oncol. https://doi.org/10.1200/JCO.2009.27.4324
19. Northcott PA, Korshunov A, Pfister SM, Taylor MD (2012) The clinical implications of medulloblastoma subgroups. Nat Rev Neurol 8:340–351. https://doi.org/10.1038/nrneurol.2012.78
20. Zou H, Poore B, Broniscer A et al (2020) Molecular heterogeneity and cellular diversity: implications for precision treatment in medulloblastoma. Cancers (Basel) 12. https://doi.org/10.3390/cancers12030643
21. Northcott PA, Buchhalter I, Morrissy AS et al (2017) The whole-genome landscape of medulloblastoma subtypes. Nature 547:311–317. https://doi.org/10.1038/nature22973
22. Northcott PA, DJH S, Peacock J et al (2012) Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 488:49–56. https://doi.org/10.1038/nature11327
23. Cavalli FMG, Remke M, Rampasek L et al (2017) Intertumoral heterogeneity within medulloblastoma subgroups. Cancer Cell. https://doi.org/10.1016/j.ccell.2017.05.005
24. Northcott PA, Robinson GW, Kratz CP et al (2019) Medulloblastoma. Nat Rev Dis Primers 5. https://doi.org/10.1038/s41572-019-0063-6
25. Kool M, Korshunov A, Remke M et al (2012) Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 123:473–484. https://doi.org/10.1007/s00401-012-0958-8
26. Kool M, Jones DTW, Jäger N et al (2014) Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell 25:393–405. https://doi.org/10.1016/j.ccr.2014.02.004
27. Batora NV, Sturm D, Jones DTW et al (2014) Transitioning from genotypes to epigenotypes: why the time has come for medulloblastoma epigenomics. Neuroscience 264:171–185. https://doi.org/10.1016/j.neuroscience.2013.07.030
28. Juraschka K, Taylor MD (2019) Medulloblastoma in the age of molecular subgroups: a review: JNSPG 75th anniversary invited review article. J Neurosurg Pediatr 24:353–363. https://doi.org/10.3171/2019.5.PEDS18381
29. Pomeroy S, Sengupta S, Pomeranz Krummel D (2017) The evolution of medulloblastoma therapy to personalized medicine. F1000Research 6:1–10. https://doi.org/10.12688/f1000research.10859.1
30. Thomas A, Noël G (2019) Medulloblastoma: optimizing care with a multidisciplinary approach. J Multidiscip Healthc 12:335–347. https://doi.org/10.2147/JMDH.S167808
31. Ramaswamy V, Taylor MD (2017) Medulloblastoma: from myth to molecular. J Clin Oncol 35:2355–2363. https://doi.org/10.1200/JCO.2017.72.7842
32. Dubuc AM, Remke M, Korshunov A et al (2013) Aberrant patterns of H3K4 and H3K27 histone lysine methylation occur across subgroups in medulloblastoma. Acta Neuropathol 125:373–384. https://doi.org/10.1007/s00401-012-1070-9
33. Clifford SC, Lusher ME, Lindsey JC et al (2006) Wnt/wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. Cell Cycle 5:2666–2670. https://doi.org/10.4161/cc.5.22.3446
34. Contributions Conceptualization A, Methodology MDT, Mor AS et al (2017) Intertumoral heterogeneity within medulloblastoma subgroups graphical abstract HHS public access. Cancer Cell 31:737–754. https://doi.org/10.1016/j.ccell.2017.05.005
35. Review N, Management C (2015) Management of and Prognosis with Medulloblastoma 65:1419–1424
36. De Braganca KC, Packer RJ, President SV, et al (2016) HHS Public Access 15:593–606. https://doi.org/10.1007/s11940-013-0255-4. Treatment
37. Remke M, Ramaswamy V (2018) Infant medulloblastoma – learning new lessons from old strata. Nat Rev Clin Oncol 15:659–660. https://doi.org/10.1038/s41571-018-0071-6
38. Collection S, De Braganca KC, Packer RJ, et al (2016) HHS Public Access 8:583–592. https://doi.org/10.1002/aur.1474. Replication
39. Pentsova EI, Shah RH, Tang J et al (2016) Evaluating cancer of the central nervous system through next-generation sequencing

of cerebrospinal fluid. J Clin Oncol 34:2404–2415. https://doi.org/10.1200/JCO.2016.66.6487
40. Liu X, Ding C, Tan W, Zhang A (2020) Medulloblastoma: molecular understanding, treatment evolution, and new developments. Pharmacol Ther 210:107516. https://doi.org/10.1016/j.pharmthera.2020.107516
41. Kufe DW, Pollock RE, Weichselbaum RR et al (eds) (2003) Holland-Frei cancer medicine, 6th edn. BC Decker Inc, Hamilton. https://www.ncbi.nlm.nih.gov/books/NBK12354/
42. Phoenix TN, Patmore DM, Boop S et al (2016) Medulloblastoma genotype dictates blood brain barrier phenotype. Cancer Cell 29:508–522. https://doi.org/10.1016/j.ccell.2016.03.002
43. Robinson GW, Orr BA, Wu G et al (2015) Vismodegib exerts targeted efficacy against recurrent sonic hedgehog – subgroup medulloblastoma: results from phase II Pediatric Brain Tumor Consortium studies PBTC-025B and PBTC-032. J Clin Oncol 33:2646–2654. https://doi.org/10.1200/JCO.2014.60.1591
44. Gajjar A, Stewart CF, Ellison DW et al (2013) Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. Clin Cancer Res 19:6305–6312. https://doi.org/10.1158/1078-0432.CCR-13-1425
45. Rudin CM, Hann CL, Laterra J et al (2009) Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med 361:1173–1178. https://doi.org/10.1056/NEJMoa0902903
46. Robinson GW, Kaste SC, Chemaitilly W et al (2017) Irreversible growth plate fusions in children with medulloblastoma treated with a targeted hedgehog pathway inhibitor. Oncotarget 8:69295–69302. https://doi.org/10.18632/oncotarget.20619
47. Kieran MW, Chisholm J, Casanova M et al (2017) Phase i study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma. Neuro-Oncology 19:1542–1552. https://doi.org/10.1093/neuonc/nox109
48. Drozdowicz K, Long J, Winterbottom E, Robbins DJ, Rodriguez-Blanco J (2017) Targeting SHH-Subgroup Medulloblastoma. JSM Brain Sci 2(2):1014
49. Dhanyamraju PKPK, Holz PSPS, Finkernagel F et al (2015) Histone deacetylase 6 represents a novel drug target in the oncogenic hedgehog signaling pathway. Mol Cancer Ther 14:727–739. https://doi.org/10.1158/1535-7163.MCT-14-0481
50. Northcott PA, Hielscher T, Dubuc A et al (2011) Pediatric and adult sonic hedgehog medulloblastomas are clinically and molecularly distinct. Acta Neuropathol 122:231–240. https://doi.org/10.1007/s00401-011-0846-7
51. Menyhárt O, Győrffy B (2020) Molecular stratifications, biomarker candidates and new therapeutic options in current medulloblastoma treatment approaches. Cancer Metastasis Rev 39:211
52. Cook Sangar ML, Genovesi LA, Nakamoto MW et al (2017) Inhibition of CDK4/6 by palbociclib significantly extends survival in medulloblastoma patient-derived xenograft mouse models. Clin Cancer Res 23:5802–5813. https://doi.org/10.1158/1078-0432.CCR-16-2943
53. El Doussouki M, Gajjar A, Chamdine O (2019) Molecular genetics of medulloblastoma in children: diagnostic, therapeutic and prognostic implications. Future Neurol 14:20–33. https://doi.org/10.2217/fnl-2018-0030
54. Blüml S, Margol AS, Sposto R et al (2016) Molecular subgroups of medulloblastoma identification using noninvasive magnetic resonance spectroscopy. Neuro-Oncology 18:126–131. https://doi.org/10.1093/neuonc/nov097
55. Dasgupta A, Gupta T, Pungavkar S et al (2019) Nomograms based on preoperative multiparametric magnetic resonance imaging for prediction of molecular subgrouping in medulloblastoma: results from a radiogenomics study of 111 patients. Neuro-Oncology 21:115–124. https://doi.org/10.1093/neuonc/noy093
56. Jones DTW, Northcott PA, Kool M, Pfister SM (2013) The role of chromatin remodeling in medulloblastoma. Brain Pathol 23:193–199. https://doi.org/10.1111/bpa.12019