



Received: 13 September, 2022

Accepted: 10 October, 2022

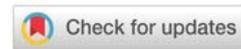
Published: 11 October, 2022

*Corresponding author: Ashfaq Ahmad, Department of Imaging and Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China, E-mail: ashfaqtajjak@hust.edu.cn

Keywords: Medulloblastoma; Central Nervous System (CNS); Magnetic Resonance Imaging (MRI); World Health Organization (WHO)

Copyright License: © 2022 Ahmad A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

<https://www.peertechzpublications.com>



Research Article

Overview of molecular subtype of medulloblastoma and role of MRI in their identification

Ashfaq Ahmad^{1-3*} and Aisha Islam⁴

¹Department of Imaging and Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

²Clinical Research Center for Medical Imaging in Hubei Province, Wuhan 430022, China

³Hubei Province Key Laboratory of Molecular Imaging, Wuhan 430022, China

⁴Department of Cardiology, Bacha Khan Medical College Mardan, KP, Pakistan

Abstract

Medulloblastoma is the most prevalent malignant brain tumor in children, accounting for roughly 15% to 20% of all malignancies of the Central Nervous System (CNS), for 40% of childhood, tumors are in the posterior fossa. Medulloblastoma is a heterogeneous combination of several subgroups with discrete characteristics, rather than a homogeneous illness. Genomic profiling of medulloblastomas revealed that the medulloblastoma may be further divided into four separate molecular subgroups. In this review, we aim to focus on the current state of understanding of the molecularly of the disease with a focus on genomic events that define the aforementioned subgroups and an overview of the molecular subtype of medulloblastoma upon discussing the following points (i) introduction to medulloblastoma and basic classification of the molecular subtype of medulloblastoma followed by their prevalence, age and gender discrimination, and specific molecular characterization. (ii) specific MRI features of the locality of a molecular subtype of medulloblastoma (iii) finally MRI distinguishable features for the identification of the specific molecular type. This review will enhance your knowledge regarding the subtype of medulloblastoma and the role of MRI in the identification of these subtypes.

Introduction

Among pediatric brain tumors, Medulloblastoma is the most common malignant brain tumor accounting for about 15% to 20% of all Central Nervous System (CNS) malignancies [1]. Although with an overall increase of survival in the last two decades about 30%, many patients still die from this disease [2]. Medulloblastoma should not be viewed as a single disease but as a heterogeneous mixture of various subgroups of distinct features. Based on their genomic profile the four distinct subgroups have been identified; Wingless (WNT), Hedgehog (SHH), Group 3 and group 4 [3,4]. In the subgroup WNT and SHH, the groups are named after their specific signal pathway involves that play an important role in the pathogenesis of that group [5]. Each of these subgroups has distinct and specific survival and genetic variation [6]. Due to a better correlation between the clinical outcome and the histological features, the World Health Organization (WHO) classified medulloblastoma into four distinct variants that are

classic, desmoplastic/nodular (D/N), Extensive nodular (MBEN) type, anaplastic and large cell and the latter often coexisting in the large cell/anaplastic (LC/A) variant [7]. Furthermore, the latest research from the medulloblastoma subjects has unveiled the presence of intertumoral heterogeneity with the existing four medulloblastoma subgroups, delineating the presence of 12 subtypes based on DNA methylation and gene expression, However, the extent of heterogeneity and overlap remains uncertain. This newly discovered variability among medulloblastoma subgroups may explain previously unexplained variation [8].

In the diagnosis, surgical guiding, and follow-up of patients with medulloblastoma, magnetic resonance imaging (MRI) plays a critical role. All patients with a brain tumor undergo an MRI [9]. Although a nonenzymatic multiplexed test for subgroup prediction is already in use [10], it could be useful and less expensive to improve the potential information that can be gleaned from a regular check-in of these patients. Prior

research has revealed that medulloblastomas can have a wide range of imaging characteristics, and that specific phenotypic radiologic traits can indicate tumor histology and biology [11-14]. These findings suggest that MRI could be a useful method for detecting medulloblastoma subtypes early [15]. Early subgroup identification may be useful in the planning of surgical resection, radiation, and chemotherapy-targeted treatments in the future. Thompson and colleagues looked at the predictive usefulness of resection extent in different subgroups [16]. After considering the molecular subgroup, the effect of increasing resection extent is considerably decreased, according to their findings.

In this review, we aim to focus on the current state of understanding of the molecularly of the disease with a focus on genomic events that define the aforementioned subgroups and an overview of the molecular subtype of medulloblastoma upon discussing the following points (i) highlight the subtypes of medulloblastoma and their distinct features, (ii) highlight the occurrence and prevalence of various subgroups, (iii) analyze the MRI features that help to predict the molecular subgroups of medulloblastoma.

Molecular classification of medulloblastoma

Up To Date classification of medulloblastoma is based primarily on morphology and includes variants such as desmoplastic/ nodular, MBEN, classic medulloblastoma, large cell, and anaplastic medulloblastoma. In the setting of a single experiment with the development of the ability to monitor transcription across the genome, various sub-groups are identified based on differences in the transcriptome [17]. The fact is that the number of subgroups of medulloblastoma among a cohort of medulloblastoma is largely dependent upon the number of individual tumors within a given cohort. With a larger cohort, an additional level of hierarchical complexity is identified [18]. Based on now-published literature and some unpublished data presented at a consensus conference in Boston, Massachusetts, members from various laboratories agreed on this that there are four principal transcriptional subgroups of medulloblastoma each of which has many subsequent structures that will be designated the sub-type of subgroup [3]. The true number of subgroups is still unknown.

The four principal subgroups of medulloblastoma are named as follows, (i) Wingless (WNT), (ii) SHH (Sonic Hedgehog), both of which were named for the signaling pathways that play a key role in the pathogenesis of that subgroup. (iii) Group 3 and (iv) Group 4.

Incidence and molecular characterization of medulloblastoma subgroup

Among the four subtypes of medulloblastoma the least common subtype is Wingless (WNT) accounts for about 10% to 11% of all medulloblastomas [19]. Overall medulloblastoma is more common in males however the sex ratio for the WNT medulloblastoma is about 1:1 (male: female) and may occur in all ages [3]. The peak incidence is usually shown at the age of 10 - 12 years and is very rare in infants [3]. From the Paul Gibson, et al. mouse model of Wnt medulloblastoma, it is suggested that

The origin of Wnt medulloblastoma is from the lower rhombic lip (LRL) of the cerebellum and embryonic dorsal brainstem than in the upper rhombic lip (URL) [20]. The overall survival (OS) in a patient with the WNT subtype had better overall survival ($p = 0.028$) than others in China as reported by Zhen-Yu Zhang, et al. [21]. The most common histology is classic histology, with uncommon occurrences of LC/A variation and metastatic spread [22]. The somatic activating mutations in exon 3 of β -catenin (CTNNB1), seen in 85 percent of WNT medulloblastoma and prognostic of a positive prognosis, are the signature alteration in WNT malignancies [23]. However, the biological effects of Wnt/ β -catenin signaling activation, as well as the link to a better prognosis, are still unknown [24].

The Sonic hedgehog subgroup (SHH) is named after the Sonic hedgehog signaling pathway. Subgroup SHH represents 28% - 30% of all medulloblastomas more common in infants (0 - 3 years) and adults (> 16 years) with much less frequent in children (3 - 16 years) [3], with a slight predominance in males among infants [25]. These individuals have an intermediate prognosis, with 5 - year survival rates ranging from 60% to 80%, however, mutations in the MYCN or TP53 oncogenes make the prognosis worse [18]. Postoperative primary radiation therapy was found as a strong prognostic factor influencing the survival in all subtypes including SHH ($p = 0.049$) in China [21]. Patients with Gorlin syndrome who have a PTCH1 germline mutation are more likely to develop basal cell carcinoma and medulloblastoma, particularly MBEN [26]. Patients with Fanconi anemia have been observed to have an unusual presentation of SHH subgroup medulloblastomas [27].

The Subgroup Group 3 tumors are mostly classic medulloblastoma, accounting for 25% to 28% of all medulloblastomas but the patients in Group 3 subgroup have the worst survival and highest rate of metastatic dissemination [28]. Medulloblastomas with a large cell/anaplastic morphology and overexpression of the cellular c-MYC gene are extremely aggressive and have a bad prognosis. This so-called MYC-subgroup differs from other types of medulloblastoma in terms of histology, gene expression profile, and clinical behavior [29]. Despite these Group 3 medulloblastoma are very rare in adults with a male-to-female ratio of 2 ratios 1 [22]. The tumor genome is significantly unbalanced, with a high number of wide changes such as the gain of chromosome 7 and iso-chromosome 17q and the primary histology is classic or LC/A. There have also been reports of links to neurocutaneous syndromes such as tuberous sclerosis complex [30].

The most common subgroup among all the medulloblastoma subgroups is Group 4 which accounts for about 34% to 35% [19]. This group has a rare incidence in infants and peaks in 10 years-old children with a high prevalence in males with a 3 ratio 1. They can have LC/A or classic histology [22]. The prognosis for Group 4 medulloblastomas is moderate, with a high probability of metastasis and relapse: In contrast to the SHH subgroup, MYCN amplification is not linked to the poorest outcome [31].

MRI features for the histologic subtype of medulloblastoma

The first important and key step in the qualitative

evaluation of tumor and extension for medulloblastoma differential diagnosis with other tumors is conventional MRI with morphological sequence. Advanced MRI features such as diffusion-weighted imaging (DWI) with an apparent diffusion coefficient (ADC) map are used for this purpose. A recent study by Yeom, et al. demonstrated the use of ADC and other MRI-specific features having distinguishability among medulloblastoma subtype and their correct diagnosis and prognosis [9]. Many studies demonstrate that medulloblastoma presents heterogeneous imaging features including comprising site and enhancement characteristics [9].

WNT medulloblastoma

A recent single study of 143 Children by Patay Z, et al. affected by medulloblastoma focused on 16 WNT tumors aims to highlight specific Wnt-subtype MRI features, correlated with its embryologic origin [32]. WNT tumors appear to form an oblique-curved triangle centered on the foramen of Luschka, with one peak reaching ventrolaterally to the CP-angle cistern, another poster-infero-medially to the cisterna magna, and a third poster-supero-medially to the fourth ventricle. WNT tumors are found in the midline and always invade the dorsal brain stem, according to previous research. The tumor's epicenter was important in the evaluation, but pre- and postoperative imaging also revealed tumor signal, cyst, necrosis, and hemorrhage. WNT tumors seemed to be extra-parenchymal and adhered to the surface of the brain stem and/or cerebellum in the majority of cases. Some of the structures invaded were the dentate nucleus, superior and middle cerebellar peduncles, lateral brain stem, an infero-medial section of the cerebellar hemisphere, and the floor of the fourth ventricle as suggested by the other studies [20,32]. Another study by Perrault, et al. about the analysis of distinctive MRI features to predict subtypes of medulloblastoma. According to their model tumor location was a key feature predictive of molecular subtype [15] but should not be generalized to the medulloblastoma subtype as demonstrated by Wan-Yee Teo, et al. study [33]. The distinct MRI feature that supports the presence of a WNT tumor is an oblique-curved triangle centered on the foramen of Luschka, tumor location, mostly one peak reaching ventrolaterally to the CP-angle cistern, another poster-infero-medially to the cisterna magna, and a third poster-supero-medially to the fourth ventricle. The important locations for WNT were the cuneate nucleus

Sonic Hedgehog (SHH)

According to Perreault, et al. study, SHH most commonly involved the cerebellar hemispheres (54 percent) [15] and the preferential localization of SHH medulloblastomas in the cerebellar hemispheres, following the higher frequency of D/N medulloblastomas involvement in this site, appears to be justified by SHH tumor origins [32] whereas cochlear nucleus onset of SHH medulloblastomas in younger patients is not supported by a different SHH tumor location between infants and older patients [20,34]. A recent research looked at a sample of 71 medulloblastoma patients to see if there was a link between genetic groupings and location [35]. In the Wefers K, et al. study an important observation was that among all the

subgroups including some tumors that were extracerebellar (37.5% WNT, 9.5% SHH, 13.3% Group 3, 22.2% Group 4), only SHH medulloblastoma presented tumors that were only intracerebellar (52.4%) [35].

As previously stated, just about half of SHH tumors (48%) had contact with the brain stem or an intraventricular growth (19 percent). All other subgroups had this contact at all times: the important locations for WNT were the cuneate nucleus and the cuneate and cochlear nuclei for Group 3 and Group 4, respectively. Infiltration of the fourth ventricle was seen in practically every case (87.5 percent WNT, 100 percent Group 3, and Group 4) [36]. The prominent proliferation in the rostral cerebellar hemisphere region of SHH tumors led to the notion that granule cells in this location may be more prone to oncogenic changes, which was supported by prior research. This research also looked at the changes in SHH type between different age groups, describing a normal two-peak age distribution. According to research, the majority of SHH medulloblastomas develop in newborns (38.1 percent) or young adults (16 years; 47.6%), whereas few SHH tumors arise in children (> 3 to 16 years; 14.3%) [37]. Wefers, et al. also describe two unique SHH medulloblastoma age entities, in which differences in location between pediatric-adult and baby SHH medulloblastomas represent different gene expression patterns and, as a result, discrete cells of origin [25,36]. The distinctive feature of SHH is most of the time about 52% is intracerebellar, had contact with the brain stem, or an intraventricular growth.

Group 3 and Group 4

Among other molecular subtypes of medulloblastoma, Group 3 tumors have worse survival independent of the metastatic stage [4,38]. With respect to the Group 3 and Group 4 medulloblastoma subtype correlation and location, it is mentioned that the origin of molecular medulloblastoma subgroup 3 and Group 4 had a 73% and 70% respectively, vermian localization [35] with the relationship between the molecular subtype of medulloblastoma and brain stem, there is always a correlation between them or with an intraventricular expansion contact and fourth ventricle infiltration for Group 3 and Group 4, the cuneate nucleus and the cochlear nucleus were contacted [36]. The important distinguishable observation between Group 3 and Group 4 medulloblastoma is that Group 4 is characteristically non-enhancing in the midline/fourth ventricle site tumors [15]. The clinical significance of determining the nature of the barrier between Groups 3 and 4 is that results differ, particularly in the case of upfront metastatic spread [16].

Finally, more sophisticated sequences might be employed to look for molecular medulloblastoma subgroup associations. In Group 3 medulloblastoma, recent research looked at the function of angiogenesis to find clinically useful biomarkers of tumor vascularity and survival. The researchers used a 7 T magnet to scan Group 3 xenografts implanted in nude rats using dynamic susceptibility-weighted perfusion (DSC) and susceptibility-weighted imaging (SWI) [39]. Vessel density and VEGFA rat protein expression were linked with imaging parameters. VEGFA mRNA expression was shown to be



considerably higher in Group 3 medulloblastoma, according to the researchers. VEGFA mRNA expression was shown to have a substantial impact on overall survival in this cohort, with low VEGFA values connected with a survival advantage and high VEGFA values correlated with a survival disadvantage. DSC MRI readings were shown to be strongly linked to vascularity and survival. A significant biomarker for survival was SW MRI with ferumoxytol. The authors concluded that DSC MRI and SWI were clinically useful indicators for tumor vascularity and overall survival in patients with Group 3 medulloblastoma and might be used to guide the use of intervascular treatments. The important location for Group 3 and Group 4 is the cuneate and cochlear nuclei respectively from where the presence of Medulloblastoma subgroups 3 and 4 can be predicted.

Conclusion

The main features of this review can be summarized as follow. (i) The number of medulloblastoma subgroups within a cohort is mostly determined by the number of individual tumors within that cohort. With a bigger cohort, there is a higher level of hierarchical complexity. (ii) the true classification of medulloblastoma up to date is classified into 4 molecular subgroups (WN, SHH Group 3 and Group 4). (iii) among the 4 subtypes of medulloblastoma, Group 3 has worse survival irrespective of metastatic stage. (iv) specific MRI features such as the shape of the tumor, tumor location, and enhancement pattern are important and well-established tools to distinguish between the different molecular subtypes of medulloblastoma.

References

- Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol*. 2015 Oct;17 Suppl 4(Suppl 4):iv1-iv62. doi: 10.1093/neuonc/nov189. Epub 2015 Oct 27. PMID: 26511214; PMCID: PMC4623240.
- Yazigi-Rivard L, Masserot C, Lachenaud J, Diebold-Pressac I, Aprahamian A, Avran D, Doz F. Le médulloblastome de l'enfant [Childhood medulloblastoma]. *Arch Pediatr*. 2008 Dec;15(12):1794-804. French. doi: 10.1016/j.arcped.2008.09.021. Epub 2008 Nov 7. PMID: 18995998.
- Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012 Apr;123(4):465-72. doi: 10.1007/s00401-011-0922-z. Epub 2011 Dec 2. PMID: 22134537; PMCID: PMC3306779.
- Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P, Rutka JT, Pfister S, Taylor MD. Medulloblastoma comprises four distinct molecular variants. *J Clin Oncol*. 2011 Apr 10;29(11):1408-14. doi: 10.1200/JCO.2009.27.4324. Epub 2010 Sep 7. PMID: 20823417; PMCID: PMC4874239.
- Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, Shih DJ, Luu B, Dubuc AM, Northcott PA, Schüller U, Gururangan S, McLendon R, Bigner D, Fouladi M, Ligon KL, Pomeroy SL, Dunn S, Triscott J, Jabado N, Fontebasso A, Jones DT, Kool M, Karajannis MA, Gardner SL, Zagzag D, Nunes S, Pimentel J, Mora J, Lipp E, Walter AW, Ryzhova M, Zheludkova O, Kumirova E, Alshami J, Croul SE, Rutka JT, Hawkins C, Tabori U, Codisposi KE, Packer RJ, Pfister SM, Korshunov A, Taylor MD. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. *Lancet Oncol*. 2013 Nov;14(12):1200-7. doi: 10.1016/S1470-2045(13)70449-2. Epub 2013 Oct 17. Erratum in: *Lancet Oncol*. 2014 Apr;15(4):e154. PMID: 24140199; PMCID: PMC3953419.
- Shih DJ, Northcott PA, Remke M, Korshunov A, Ramaswamy V, Kool M, Luu B, Yao Y, Wang X, Dubuc AM, Garzia L, Peacock J, Mack SC, Wu X, Rolider A, Morrissy AS, Cavalli FM, Jones DT, Zitterbart K, Faria CC, Schüller U, Kren L, Kumabe T, Tominaga T, Shin Ra Y, Garami M, Hauser P, Chan JA, Robinson S, Bognár L, Klekner A, Saad AG, Liau LM, Albrecht S, Fontebasso A, Cinalli G, De Antonellis P, Zollo M, Cooper MK, Thompson RC, Bailey S, Lindsey JC, Di Rocco C, Massimi L, Michiels EM, Scherer SW, Phillips JJ, Gupta N, Fan X, Muraszko KM, Vibhakar R, Eberhart CG, Fouladi M, Lach B, Jung S, Wechsler-Reya RJ, Fèvre-Montange M, Jouvét A, Jabado N, Pollack IF, Weiss WA, Lee JY, Cho BK, Kim SK, Wang KC, Leonard JR, Rubin JB, de Torres C, Lavarino C, Mora J, Cho YJ, Tabori U, Olson JM, Gajjar A, Packer RJ, Rutkowski S, Pomeroy SL, French PJ, Kloosterhof NK, Kros JM, Van Meir EG, Clifford SC, Bourdeaut F, Delattre O, Doz FF, Hawkins CE, Malkin D, Grajkowska WA, Perek-Polnik M, Bouffet E, Rutka JT, Pfister SM, Taylor MD. Cytogenetic prognostication within medulloblastoma subgroups. *J Clin Oncol*. 2014 Mar 20;32(9):886-96. doi: 10.1200/JCO.2013.50.9539. Epub 2014 Feb 3. PMID: 24493713; PMCID: PMC3948094.
- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016 Jun;131(6):803-20. doi: 10.1007/s00401-016-1545-1. Epub 2016 May 9. PMID: 27157931.
- Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B, Garzia L, Torchia J, Nor C, Morrissy AS, Agnihotri S, Thompson YY, Kuzan-Fischer CM, Farooq H, Isaev K, Daniels C, Cho BK, Kim SK, Wang KC, Lee JY, Grajkowska WA, Perek-Polnik M, Vasiljevic A, Faure-Contier C, Jouvét A, Giannini C, Nageswara Rao AA, Li KKW, Ng HK, Eberhart CG, Pollack IF, Hamilton RL, Gillespie GY, Olson JM, Leary S, Weiss WA, Lach B, Chambless LB, Thompson RC, Cooper MK, Vibhakar R, Hauser P, van Veelen MC, Kros JM, French PJ, Ra YS, Kumabe T, López-Aguilar E, Zitterbart K, Sterba J, Finocchiaro G, Massimino M, Van Meir EG, Osuka S, Shofuda T, Klekner A, Zollo M, Leonard JR, Rubin JB, Jabado N, Albrecht S, Mora J, Van Meter TE, Jung S, Moore AS, Hallahan AR, Chan JA, Tirapelli DPC, Carlotti CG, Fouladi M, Pimentel J, Faria CC, Saad AG, Massimi L, Liau LM, Wheeler H, Nakamura H, Elbabaa SK, Perezpeña-Diazconti M, Chico Ponce de León F, Robinson S, Zapotocky M, Lassaletta A, Huang A, Hawkins CE, Tabori U, Bouffet E, Bartels U, Dirks PB, Rutka JT, Bader GD, Reimand J, Goldenberg A, Ramaswamy V, Taylor MD. Intertumoral Heterogeneity within Medulloblastoma Subgroups. *Cancer Cell*. 2017 Jun 12;31(6):737-754.e6. doi: 10.1016/j.ccell.2017.05.005. PMID: 28609654; PMCID: PMC6163053.
- Yeom KW, Mobley BC, Lober RM, Andre JB, Partap S, Vogel H, Barnes PD. Distinctive MRI features of pediatric medulloblastoma subtypes. *AJR Am J Roentgenol*. 2013 Apr;200(4):895-903. doi: 10.2214/AJR.12.9249. PMID: 23521467.
- Northcott PA, Shih DJ, Remke M, Cho YJ, Kool M, Hawkins C, Eberhart CG, Dubuc A, Guettouche T, Cardentey Y, Bouffet E, Pomeroy SL, Marra M, Malkin D, Rutka JT, Korshunov A, Pfister S, Taylor MD. Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. *Acta Neuropathol*. 2012 Apr;123(4):615-26. doi: 10.1007/s00401-011-0899-7. Epub 2011 Nov 6. PMID: 22057785; PMCID: PMC3306784.
- Albright L. Posterior fossa tumors. *Neurosurg Clin N Am*. 1992 Oct;3(4):881-91. PMID: 1392582.
- Koeller KK, Rushing EJ. From the archives of the AFIP: medulloblastoma: a comprehensive review with radiologic-pathologic correlation. *Radiographics*. 2003 Nov-Dec;23(6):1613-37. doi: 10.1148/rg.236035168. PMID: 14615567.
- Rasalkar DD, Chu WC, Paunipagar BK, Cheng FW, Li CK. Paediatric intra-axial posterior fossa tumours: pictorial review. *Postgrad Med J*. 2013 Jan;89(1047):39-46. doi: 10.1136/postgradmedj-2011-130075. Epub 2012 Sep 12. PMID: 22977284.
- Choudhri AF, Siddiqui A, Klimo P Jr. Pediatric Cerebellar Tumors: Emerging Imaging Techniques and Advances in Understanding of Genetic Features. *Neuroimaging Clin N Am*. 2016 Aug;26(3):459-69. doi: 10.1016/j.nic.2016.03.010. PMID: 27423803.
- Perreault S, Ramaswamy V, Achrol AS, Chao K, Liu TT, Shih D, Remke M, Schubert S, Bouffet E, Fisher PG, Partap S, Vogel H, Taylor MD, Cho YJ, Yeom



- KW. MRI surrogates for molecular subgroups of medulloblastoma. *AJNR Am J Neuroradiol.* 2014 Jul;35(7):1263-9. doi: 10.3174/ajnr.A3990. Epub 2014 May 15. PMID: 24831600; PMCID: PMC4819007.
16. Thompson EM, Hielscher T, Bouffet E, Remke M, Luu B, Gururangan S, McLendon RE, Bigner DD, Lipp ES, Perreault S, Cho YJ, Grant G, Kim SK, Lee JY, Rao AAN, Giannini C, Li KKW, Ng HK, Yao Y, Kumabe T, Tominaga T, Grajkowska WA, Perek-Polnik M, Low DCY, Seow WT, Chang KTE, Mora J, Pollack IF, Hamilton RL, Leary S, Moore AS, Ingram WJ, Hallahan AR, Jouvett A, Fèvre-Montange M, Vasiljevic A, Faure-Conter C, Shofuda T, Kagawa N, Hashimoto N, Jabado N, Weil AG, Gayden T, Wataya T, Shalaby T, Grotzer M, Zitterbart K, Sterba J, Kren L, Hortobágyi T, Klekner A, László B, Pócza T, Hauser P, Schüller U, Jung S, Jang WY, French PJ, Kros JM, van Veelen MC, Massimi L, Leonard JR, Rubin JB, Vibhakar R, Chambless LB, Cooper MK, Thompson RC, Faria CC, Carvalho A, Nunes S, Pimentel J, Fan X, Muraszko KM, López-Aguilar E, Lyden D, Garzia L, Shih DJH, Kijima N, Schneider C, Adamski J, Northcott PA, Kool M, Jones DTW, Chan JA, Nikolic A, Garre ML, Van Meir EG, Osuka S, Olson JJ, Jahangiri A, Castro BA, Gupta N, Weiss WA, Moxon-Emre I, Mabbott DJ, Lassaletta A, Hawkins CE, Tabori U, Drake J, Kulkarni A, Dirks P, Rutka JT, Korshunov A, Pfister SM, Packer RJ, Ramaswamy V, Taylor MD. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. *Lancet Oncol.* 2016 Apr;17(4):484-495. doi: 10.1016/S1470-2045(15)00581-1. Epub 2016 Mar 12. Erratum in: *Lancet Oncol.* 2022 Feb;23(2):e59. PMID: 26976201; PMCID: PMC4907853.
 17. Pomeroy SL, Tamayo P, Gaasenbeek M, Sturla LM, Angelo M, McLaughlin ME, Kim JY, Goumnerova LC, Black PM, Lau C, Allen JC, Zagzag D, Olson JM, Curran T, Wetmore C, Biegel JA, Poggio T, Mukherjee S, Rifkin R, Califano A, Stolovitzky G, Louis DN, Mesirov JP, Lander ES, Golub TR. Prediction of central nervous system embryonal tumour outcome based on gene expression. *Nature.* 2002 Jan 24;415(6870):436-42. doi: 10.1038/415436a. PMID: 11807556.
 18. Cho YJ, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, Berhoukim R, Amani V, Goumnerova L, Eberhart CG, Lau CC, Olson JM, Gilbertson RJ, Gajjar A, Delattre O, Kool M, Ligon K, Meyerson M, Mesirov JP, Pomeroy SL. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. *J Clin Oncol.* 2011 Apr 10;29(11):1424-30. doi: 10.1200/JCO.2010.28.5148. Epub 2010 Nov 22. PMID: 21098324; PMCID: PMC3082983.
 19. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, Kenney AM, Brat DJ, Perry A, Yong WH, Taylor RE, Bailey S, Clifford SC, Gilbertson RJ. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. *Acta Neuropathol.* 2011 Mar;121(3):381-96. doi: 10.1007/s00401-011-0800-8. Epub 2011 Jan 26. PMID: 21267586; PMCID: PMC3519926.
 20. Grzybicki DM. Subtypes of medulloblastoma have distinct developmental origins. *Yearb. Pathol. Lab. Med.* 2012; 221-222.
 21. Zhang ZY, Xu J, Ren Y, Li KK, Ng HK, Mao Y, Zhong P, Yao Y, Zhou LF. Medulloblastoma in China: clinicopathologic analyses of SHH, WNT, and non-SHH/WNT molecular subgroups reveal different therapeutic responses to adjuvant chemotherapy. *PLoS One.* 2014 Jun 16;9(6):e99490. doi: 10.1371/journal.pone.0099490. Erratum in: *PLoS One.* 2014;9(8):e105742. Erratum in: *PLoS One.* 2014;9(9):e107855. PMID: 24932704; PMCID: PMC4059646.
 22. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, Cho YJ, Koster J, Schouten-van Meeteren A, van Vuurden D, Clifford SC, Pietsch T, von Bueren AO, Rutkowski S, McCabe M, Collins VP, Bäcklund ML, Haberler C, Bourdeaut F, Delattre O, Doz F, Ellison DW, Gilbertson RJ, Pomeroy SL, Taylor MD, Lichter P, Pfister SM. 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.* 2012 Apr;123(4):473-84. doi: 10.1007/s00401-012-0958-8. Epub 2012 Feb 23. PMID: 22358457; PMCID: PMC3306778.
 23. Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, Pearson AD, Clifford SC; United Kingdom Children's Cancer Study Group Brain Tumour Committee. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. *J Clin Oncol.* 2005 Nov 1;23(31):7951-7. doi: 10.1200/JCO.2005.01.5479. PMID: 16258095.
 24. Di Giannatale A, Carai A, Cacchione A, Marrazzo A, Dell'Anna VA, Colafati GS, Diomed-Camassei F, Miele E, Po A, Ferretti E, Locatelli F, Mastronuzzi A. Anomalous vascularization in a Wnt medulloblastoma: a case report. *BMC Neurol.* 2016 Jul 15;16:103. doi: 10.1186/s12883-016-0632-1. PMID: 27416922; PMCID: PMC4946170.
 25. Northcott PA, Hielscher T, Dubuc A, Mack S, Shih D, Remke M, Al-Halabi H, Albrecht S, Jabado N, Eberhart CG, Grajkowska W, Weiss WA, Clifford SC, Bouffet E, Rutka JT, Korshunov A, Pfister S, Taylor MD. Pediatric and adult sonic hedgehog medulloblastomas are clinically and molecularly distinct. *Acta Neuropathol.* 2011 Aug;122(2):231-40. doi: 10.1007/s00401-011-0846-7. Epub 2011 Jun 17. PMID: 21681522; PMCID: PMC4538327.
 26. Fujii K, Miyashita T. Gorlin syndrome (nevoid basal cell carcinoma syndrome): update and literature review. *Pediatr Int.* 2014 Oct;56(5):667-74. doi: 10.1111/ped.12461. PMID: 25131638.
 27. Miele E, Mastronuzzi A, Po A, Carai A, Alfano V, Serra A, Colafati GS, Strocchio L, Antonelli M, Buttarelli FR, Zani M, Ferraro S, Buffone A, Vacca A, Screpanti I, Giangaspero F, Giannini G, Locatelli F, Ferretti E. Characterization of medulloblastoma in Fanconi Anemia: a novel mutation in the BRCA2 gene and SHH molecular subgroup. *Biomark Res.* 2015 Jun 6;3:13. doi: 10.1186/s40364-015-0038-z. PMID: 26064523; PMCID: PMC4462002.
 28. Wang X, Dubuc AM, Ramaswamy V, Mack S, Gendoo DM, Remke M, Wu X, Garzia L, Luu B, Cavalli F, Peacock J, López B, Skowron P, Zagzag D, Lyden D, Hoffman C, Cho YJ, Eberhart C, MacDonald T, Li XN, Van Meter T, Northcott PA, Haibe-Kains B, Hawkins C, Rutka JT, Bouffet E, Pfister SM, Korshunov A, Taylor MD. Medulloblastoma subgroups remain stable across primary and metastatic compartments. *Acta Neuropathol.* 2015 Mar;129(3):449-57. doi: 10.1007/s00401-015-1389-0. Epub 2015 Jan 21. PMID: 25689980; PMCID: PMC4333718.
 29. Kawachi D, Robinson G, Uziel T, Gibson P, Rehg J, Gao C, Finkelstein D, Qu C, Pounds S, Ellison DW, Gilbertson RJ, Roussel MF. A mouse model of the most aggressive subgroup of human medulloblastoma. *Cancer Cell.* 2012 Feb 14;21(2):168-80. doi: 10.1016/j.ccr.2011.12.023. PMID: 22340591; PMCID: PMC3285412.
 30. Moavero R, Folgiero V, Carai A, Miele E, Ferretti E, Po A, Diomed Camassei F, Lepri FR, Vigeveno F, Curatolo P, Valeriani M, Colafati GS, Locatelli F, Tornesello A, Mastronuzzi A. Metastatic Group 3 Medulloblastoma in a Patient With Tuberous Sclerosis Complex: Case Description and Molecular Characterization of the Tumor. *Pediatr Blood Cancer.* 2016 Apr;63(4):719-22. doi: 10.1002/pbc.25851. Epub 2015 Dec 2. PMID: 26626406.
 31. Shih DJ, Northcott PA, Remke M, Korshunov A, Ramaswamy V, Kool M, Luu B, Yao Y, Wang X, Dubuc AM, Garzia L, Peacock J, Mack SC, Wu X, Rolider A, Morrissy AS, Cavalli FM, Jones DT, Zitterbart K, Faria CC, Schüller U, Kren L, Kumabe T, Tominaga T, Shin Ra Y, Garami M, Hauser P, Chan JA, Robinson S, Bognár L, Klekner A, Saad AG, Liau LM, Albrecht S, Fontebasso A, Cinalli G, De Antonellis P, Zollo M, Cooper MK, Thompson RC, Bailey S, Lindsey JC, Di Rocco C, Massimi L, Michiels EM, Scherer SW, Phillips JJ, Gupta N, Fan X, Muraszko KM, Vibhakar R, Eberhart CG, Fouladi M, Lach B, Jung S, Wechsler-Reya RJ, Fèvre-Montange M, Jouvett A, Jabado N, Pollack IF, Weiss WA, Lee JY, Cho BK, Kim SK, Wang KC, Leonard JR, Rubin JB, de Torres C, Lavarino C, Mora J, Cho YJ, Tabori U, Olson JM, Gajjar A, Packer RJ, Rutkowski S, Pomeroy SL, French PJ, Kloosterhof NK, Kros JM, Van Meir EG, Clifford SC, Bourdeaut F, Delattre O, Doz FF, Hawkins CE, Malkin D, Grajkowska WA, Perek-Polnik M, Bouffet E, Rutka JT, Pfister SM, Taylor MD. Cytogenetic prognostication within medulloblastoma subgroups. *J Clin Oncol.* 2014 Mar 20;32(9):886-96. doi: 10.1200/JCO.2013.50.9539. Epub 2014 Feb 3. PMID: 24493713; PMCID: PMC3948094.
 32. Patay Z, DeSain LA, Hwang SN, Coan A, Li Y, Ellison DW. MR Imaging Characteristics of Wingless-Type-Subgroup Pediatric Medulloblastoma. *AJNR Am J Neuroradiol.* 2015 Dec;36(12):2386-93. doi: 10.3174/ajnr.A4495. Epub 2015 Sep 3. PMID: 26338912; PMCID: PMC4827780.
 33. Teo WY, Shen J, Su JM, Yu A, Wang J, Chow WY, Li X, Jones J, Dauser R, Whitehead W, Adesina AM, Chintagumpala M, Man TK, Lau CC. Implications of tumor location on subtypes of medulloblastoma. *Pediatr Blood Cancer.* 2013 Sep;60(9):1408-10. doi: 10.1002/pbc.24511. Epub 2013 Mar 19. PMID: 23512859.



34. Grammel D, Warmuth-Metz M, von Bueren AO, Kool M, Pietsch T, Kretzschmar HA, Rowitch DH, Rutkowski S, Pfister SM, Schüller U. Sonic hedgehog-associated medulloblastoma arising from the cochlear nuclei of the brainstem. *Acta Neuropathol.* 2012 Apr;123(4):601-14. doi: 10.1007/s00401-012-0961-0. Epub 2012 Feb 21. PMID: 22349907.
35. Wefers AK, Warmuth-Metz M, Pöschl J, von Bueren AO, Monoranu CM, Seelos K, Peraud A, Tonn JC, Koch A, Pietsch T, Herold-Mende C, Mawrin C, Schouten-van Meeteren A, van Vuurden D, von Hoff K, Rutkowski S, Pfister SM, Kool M, Schüller U. Subgroup-specific localization of human medulloblastoma based on pre-operative MRI. *Acta Neuropathol.* 2014;127(6):931-3. doi: 10.1007/s00401-014-1271-5. Epub 2014 Apr 4. PMID: 24699697.
36. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, Castelo-Branco P, Baskin B, Ray PN, Bouffet E, von Bueren AO, Jones DT, Northcott PA, Kool M, Sturm D, Pugh TJ, Pomeroy SL, Cho YJ, Pietsch T, Gessi M, Rutkowski S, Bogner L, Klekner A, Cho BK, Kim SK, Wang KC, Eberhart CG, Fevre-Montange M, Fouladi M, French PJ, Kros M, Grajkowska WA, Gupta N, Weiss WA, Hauser P, Jabado N, Jouvett A, Jung S, Kumabe T, Lach B, Leonard JR, Rubin JB, Liau LM, Massimi L, Pollack IF, Shin Ra Y, Van Meir EG, Zitterbart K, Schüller U, Hill RM, Lindsey JC, Schwalbe EC, Bailey S, Ellison DW, Hawkins C, Malkin D, Clifford SC, Korshunov A, Pfister S, Taylor MD, Tabori U. Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. *J Clin Oncol.* 2013 Aug 10;31(23):2927-35. doi: 10.1200/JCO.2012.48.5052. Epub 2013 Jul 8. PMID: 23835706; PMCID: PMC4878050.
37. Kool M, Jones DT, Jäger N, Northcott PA, Pugh TJ, Hovestadt V, Piro RM, Esparza LA, Markant SL, Remke M, Milde T, Bourdeaut F, Ryzhova M, Sturm D, Pfaff E, Stark S, Hutter S, Seker-Cin H, Johann P, Bender S, Schmidt C, Rausch T, Shih D, Reimand J, Sieber L, Wittmann A, Linke L, Witt H, Weber UD, Zapatka M, König R, Beroukheim R, Bergthold G, van Sluis P, Volckmann R, Koster J, Versteeg R, Schmidt S, Wolf S, Lawerenz C, Bartholomae CC, von Kalle C, Unterberg A, Herold-Mende C, Hofer S, Kulozik AE, von Deimling A, Scheurlen W, Felsberg J, Reifenberger G, Hasselblatt M, Crawford JR, Grant GA, Jabado N, Perry A, Cowdrey C, Croul S, Zadeh G, Korbel JO, Doz F, Delattre O, Bader GD, McCabe MG, Collins VP, Kieran MW, Cho YJ, Pomeroy SL, Witt O, Brors B, Taylor MD, Schüller U, Korshunov A, Eils R, Wechsler-Reya RJ, Lichter P, Pfister SM; ICGC PedBrain Tumor Project. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothed inhibition. *Cancer Cell.* 2014 Mar 17;25(3):393-405. doi: 10.1016/j.ccr.2014.02.004. PMID: 24651015; PMCID: PMC4493053.
38. Ellison DW, Onilude OE, Lindsey JC, Lusher ME, Weston CL, Taylor RE, Pearson AD, Clifford SC; United Kingdom Children's Cancer Study Group Brain Tumour Committee. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. *J Clin Oncol.* 2005 Nov 1;23(31):7951-7. doi: 10.1200/JCO.2005.01.5479. PMID: 16258095.
39. Thompson EM, Keir ST, Venkatraman T, Lascola C, Yeom KW, Nixon AB, Liu Y, Picard D, Remke M, Bigner DD, Ramaswamy V, Taylor MD. The role of angiogenesis in Group 3 medulloblastoma pathogenesis and survival. *Neuro Oncol.* 2017 Sep 1;19(9):1217-1227. doi: 10.1093/neuonc/nox033. PMID: 28379574; PMCID: PMC5570262.