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Research Article

Molecular Biology of the two Most Common Brain Neoplasms in Adults and Pediatric Population - An Essential Review

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Abstract

Brain neoplasms are one of the most principal causes of morbidity and mortality in a wide range of individuals. Gliomas consist the most conventional primary intracranial tumors in adult individuals and are characterized by an extremely poor prognosis. Other less common brain neoplasms concern meningiomas, medulloblastomas, Central Nervous System lymphomas, hemangioblastomas, etc. They appear in diverse location of the CNS and affect adults and pediatric population. Meningioma (MG) is a typically benign brain tumor, the most common primary brain tumor, accounting for more than 40% of all brain tumors. MGs originate in the meninges, and about 80% are benign, slow-growing tumors, whereas 20% show malignant signs in their histology and correspond to grade II or III.

Moreover, in some cases MGs can be persistent and recurrent after treatment. Recent advances in genetics and epigenetics have detected molecular alterations which drive MG biology with prognostic and therapeutic implications. Medulloblastoma (MB) is the most common primary embryonal pediatric malignant brain tumor composed of four molecular subgroups, wingless type (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4, with distinct histological and molecular profiles, and a significant contributor to pediatric morbidity and mortality. However, recent molecular findings led to the WHO updating their guidelines and classifying MBs into further molecular subgroups, changing the clinical stratification and treatment management. The tumor occurs in association with two inherited cancer syndromes, Turcot and Gorlin syndrome. Insights into the molecular biology of the tumor concern alterations in the genes altered in those syndromes, PTC and APC, respectively. With regard to anatomical routes of spreading, an hematogenous route for MB metastasis has recently been demonstrated, whereas sequencing studies identified novel mutations involved in the cyclic AMP-dependent pathway or RNA processing in the Sonic Hedgehog (SHH) subgroup, and core-binding factor subunit alpha (CBFA) complex in the 4 sub-group. The molecular biology of the mentioned neoplasms is a complicated and fast-developing field in which basic research is necessary to meet clinical expectations in terms of antitumor effectiveness. Many investigations contributed to advancement in the knowledge of their pathogenesis and biology and to the detection of new agents for personalized targeted molecular therapy. Despite the progress in molecular biology, significant contribution to the overall survival and life quality still lacks. The present study presents a comprehensive review of current knowledge regarding the molecular features of the mentioned neoplasms from the molecular biology perspective, focused on the main intracellular signaling pathways involved in their pathogenesis, genomic and epigenetic relevant characteristics, the predictive values of molecular indices according to the WHO classification.

Key Words: meningioma; medulloblastoma; molecular biology; genetics; epigenetics

Introduction

Brain neoplasms affect a wide range of individuals and consist main causes of morbidity and mortality, globally. Among them some types are considered as the most common ones in adults and pediatric population, and concern MGs and MBs, respectively. MGs represent up to 40% of all primary CNS tumors, and are considered the most frequent primary intracranial tumors [1,2]. The actual cell of their origin remains unknown despite the fact that it was considered to be derived from arachnoid cap cells due to cytological similarities [3,4]. Approximately 80% are benign lesions and correspond to grade I according to the WHO classification, whereas 20% show malignant signs in their histology and correspond to grade II or III [2]. The WHO classification system has determined 15 different MG variants, nine grade I, three grade II, and three grade III [2]. The characteristic genetic alterations concern loss of chromosome 22q [5-7],14q [8],18q [9,10],CDKN2/AB 2A/B [11-16] homozygous deletions, germline mutations such as mutations of NF2 gene [11,17-30], SMO and SUFU [29-40], SMARCE1 [6,41-44], somatic mutations such as KLF4 mutations [15,24,25,44-48], TRAF7 [24,26,38,49-53], TERT promoter [15,54-59], AKT1 [60-65], and PIK3CA mutations in the phosphatidyl-inositol-3kinase (PI3K) pathway[66-69], mutations of RNA polymerase II subunit A [26], BRCA1-associated protein (BAP1) mutations [70-72], Duchenne Muscular Dystrophy mutations (DMD) [73-76], Polybromo-1 (PBRM1) mutations [77-79], epigenetic alterations such as H3K27me3 alterations [80-85], methylation of TIMP3 [9,86-89] and TP73 promoter (TP73p) [87,90-92].

MB has an incidence of 2 to 5 cases per 10,000 population per year, leading to approximately 240 new cases per year in the United States [93]. Most MBs appear sporadically, although the tumor may arise rarely as part of an inherited cancer syndrome, such as Turcot and Gorlin syndrome [94-97]. Only one karyotypic abnormality has been detected to be typical of MB, the isochromosome 17q, which is present in approximately 50% of tumors [98,99]. Other Growth Factor signaling pathways which are involved in MB concern the erbB family members expression, erbB2 and erbB4 [100], and IGF-1R activation [101]. Moreover, epigenetic alterations [102] are also implicated in its pathogenesis. Progress in cancer research concerning the genetics and molecular biology of malignant brain tumors has been substantially increased in the past decades, resulting in the classification methods which could contribute to management and classification of those patients into different groups. Many efforts contributed to advancement in the knowledge of their pathogenesis and biology and to the detection of new agents for personalized targeted molecular treatment. However, despite the progress in molecular biology, significant contribution to the overall survival rate and life quality still remains disappointing.

The present research presents a comprehensive review of current knowledge regarding the molecular features of tumorigenesis from the molecular biology perspective, focused on the principal intracellular signaling pathways involved in their pathogenesis, and the genomic and epigenetic relevant characteristics the two most common brain neoplasms in adults and paediatric population, MG and MB, respectively.

Meningiomas

The actual cell of MG origin remains unknown, as already mentioned, however it is possible that the tumors are derived from arachnoid barrier cells, since MGs and arachnoid barrier cells have shared expression of Prostaglandin D synthase [103]. Moreover, MGs are one of the most frequent tumors which appear after radiation therapy, especially in the pediatric population [104], and have a tendency to behave more aggressively than sporadic ones and often rise two decades after radiotherapy [105].

Molecular alterations of meningiomas – Copy number alterations

Chromosome 22q Loss

Somatic Copy Number Alterations (CNAs) seem to play an essential role in MG-genesis by dysregulating oncogene and tumor suppressor activity [8]. A cytogenetic study, showed a G-group chromosome loss, either chromosome 21 or 22, in all tumor samples under examination and multiple chromosomal abnormalities in 50% of the samples examined [8]. Another report confirmed the increased incidence of monosomy 22 in MG cases [106]. Spinal and convexity MGs mainly harbor 22q loss, whereas skull-base ones are characterized by other frequent mutations [107]. Studies which investigated the loss of heterozygosity (LOH) showed that chromosome 22q was lost in 60% to 70% of sporadic MG cases [6]. That 22q LOH incidence increases with WHO grade, with a 50% prevalence in WHO grade I tumors and 75% to 85% prevalence in WHO grades II and III tumors [6]. Hong *et al.* [108], showed a novel mutation concurrent with 1p/22q codeletion in a case with multiple recurrent MGs responding to sunitinib. The first finding of a specific genetic etiology of MGs was the identification of alterations in the tumor suppressor gene NF2, localized on chromosome 22, which encodes the protein merlin [109]. (Table 1)

Chromosome 1p Loss

The second most common alteration in those tumors is the chromosome 1p deletion, which is mainly related to higher WHO grade. Moreover, 1p loss is regarded as an early event in the malignant progression of MGs [110], and most frequently involves the 1p33-34 and 1p36 regions, which may are responsible for methylation-mediated inactivation of ALPL and TP73 genes [111].Another study which examined 124 samples come from 105 tumor cases, in WHO grade I MGs, 1p36 loss was identified in 27.4%, in grade II in 37.1% and in anaplastic tumor in 87.5% of cases. The authors also showed that accumulated CNAs, such as the 1p/14q co-alteration, have been suggested to increase the risk of malignant behavior of sporadic MGs [112]. Combined 1p/14q deletions were detected in 7 percentage benign, 39percentage atypical, and 63percentage anaplastic MGs (p Less-than 0.001) [110]. (Table 1)

Chromosome 14q Loss

Chromosome 14q loss is implicated in the pathological progression of MG, however, the specific mechanism remains unknown. Another study considered that 14q loss resulted in low transcript expression of the tumor suppressor gene NDRG2 at 14q11.2, thereby playing an essential role in MG progression [113]. A retrospective clinical study showed that 14q loss was associated with higher tumor invasiveness and recurrence risk in MGs of all pathological grades [114]. A similar article by Balik *et al.* [115] showed that maternally expressed 3 (MEG3), a long non-coding RNA on 14q, suppressed MG growth to a certain degree, but further relevant clinical trials are required. Gupta *et al.* [116], recorded the results from 46 MG cases in a single-center retrospective clinical study, and reported an association between 14q loss and a high mitotic index of tumors (pLess-than0.05). Krayenbühl *et al.* [117], compared differences between *de novo* malignant MGs and those which progressed to malignancy, and were found an increased chromosome 14 monosomy. (Table 1)

Chromosome 18q Loss

Chromosome 18q loss in MGs has been considered as indicator of poor prognosis [9]. Although the mentioned loss was initially localized at the end of 18q22, the specific mechanism of that alteration in tumor progression remains unclear. In another research with 90 MG samples [10], 18q loss was detected in up to 43% of WHO grade II MGs. (Table 1)

Chromosome 6q, 17q and 20q Loss

The mentioned chromosomes deletions more commonly have been observed in high-grade MGs when compared to low-grade ones [118]. (Table 1)

Gene mutation signatures (Germline mutations)

Mutations of NF2 gene

The NF2 gene is localized on chromosome 22q12.2, contains 17 exons, and encodes for a69 kDa protein, known as merlin [17], which acts as a tumor suppressor gene by inhibiting cell growth through contact inhibition and consequent activation of multiple pathways [109]. Sporadic mutations in the NF2 gene are implicated in 40% to 60% of MG cases [18], whereas 50% to 75% of patients with germline mutations develop MGs [19]. NF2 gene loss is a driver mutation commonly implicated in high-grade MGs [20]. NF2 loss-of -function mutations occur through a double-hit mechanism in those tumors, either through a germline mutation and a second hit with a somatic one in syndromic cases, or with a somatic single nucleotide variation or insertion/deletion mutation and an overlapping chromosome 22 deletion event as frequently detected in sporadic cases [20]. 95% of NF2-associated tumors remain grade I, the presence of an NF2 mutation has been associated with increased tumor size and cell proliferation, and it has been suggested that NF2 loss may be the primary and sole initiator of MG-genesis in both cranial and spinal types [21].

Moreover, the NF2 mutation plays an essential role in the tumor pathogenesis by activating the mammalian target of rapamycin (mTOR) biological signaling pathway through mTOR complex 1 (mTORC1) modulation [22,23]. Those mutations, in general, are related to convexity MGs rather than the anterior skull base ones [24]. NF2-mutated MGs were frequently detected in the spinal cord and non-skull base locations after performing a sequencing analysis of 3,016 cases [25]. Focal NF2 inactivating mutations were observed in 40% to 60% of sporadic tumors and revealed in MGs of all three histopathological grades [6,24,26]. Another research by Wellen Reuther *et al.* [27] showed that NF2 mutations mainly appear in fibrous (70%) and transitional (83%) subtypes after sequencing a cohort of 70 MG cases.

A single-center retrospective study [28] examined 103 tumors and found that the recurrence risk ratio of NF2-mutated MGs was significantly increased compared with that of NF2 wild-type tumors (p=0.037). Similar findings were confirmed by Youngblood *et al.* [29]. After analyzing the genomic data from 850 refractory MG cases, Williams *et al.* [30], showed that the NF2-mutated type was the most frequent (50%) and was related to the male gender (64.4%). Other additional mutations were also identified and concerned CDKN2A/B (24%) and chromatin remodeling factor genes ARID1A (9%), and KDM6A (6%). In murine models, increasing chromosomal instability because of homozygous loss, inactivation, or point mutation in NF2 together with CDKN2A/B were able to promote the tumor growth [11,30]. (Table 1)

SMO and SUFU mutations in the Hedgehog signaling pathway

The SUFU gene, a tumor suppressor gene, is localized on chromosome 10, specifically in the region 10q24-25. SUFU plays an essential role in regulating the Sonic Hedgehog (SHH) signaling pathway, and its loss of function can disrupt this pathway, contributing to tumor development [31,32]. Germline disruptions in SUFU are also regarded to predispose to initiation of diverse types of cancer, such as basal cell carcinoma, gonadal tumors, and MGs [31]. Moreover, SUFU mutations have been linked with the development of isolated familial MGs and multiple ones [33]. In a study in which investigated four related family members [34], three of which had an history of the tumor, was detected a frameshift mutation in SUFU leading to a premature stop codon and it was suggested to be associated with MGs development. Alterations in SUFU lead to the Hedgehog (Hh) signaling pathway dysregulation, the activation of which has been found to play an essential role in MG growth and development, with 72% of Hh pathway genes being differentially expressed in MGs compared with normal tissue [35]. After genomic analyzing of 850 MG cases, SUFU mutations were revealed in 23 cases and was observed to co-occur with PTEN and ARID1A mutations [30]. SMO is a G-protein coupled receptor involved in the Hh signaling pathway [36]. SMO mutations have been detected in 3% to 6% of all MGs, 28% of old factory groove MGs, and 11% of anterior skull base ones [37-40]. Compared with AKT1 mutations-MGs, SMO-mutated old factory groove MGs showed higher recurrence rates, and when compared with AKT1-mutated or wild-type tumors, SMO-mutated anterior skull base MGs showed significantly larger tumor size [39,40]. SMO^{L412F} and SMO^{W535L} mutations were observed in 3% to 6% of MGs mainly appearing in the anterior midline skull base [25,29,37]. (Table 1)

SMARCE1 mutations

Germline mutations in two SWI/SNF chromatin remodeling complex subunits, SMARCB 1 and SMARCE1 have also been involved in MG-genesis [41]. Mutations in SMARCB1 have been associated with the development of multiple MGs, whereas SMARCE1 loss of function mutations have been involved in patients with familial multiple spinal MGs with clear-cell histology [6,41-43]. MGs of spinal Ord showed SMARCE1 mutations, whereas other mutations are rare in that location [42]. (Table 1)

CDKN2A/B homozygous deletions

The Cyclin-dependent Kinase Inhibitor A and B (CDKN2A/B) gene, which is localized at 9p21.3, regulates the cell cycle and functions as a tumor suppressor gene [16]. Except NF2 inactivation, CDKN2A/B loss seems to contribute to MG progression and has been linked with shorter time to recurrence in mice [11]. CDKN2A and CDKN2B homozygous losses have been found to be linked with an increased MG frequency in murine models inactivated for the NF2 gene [11]. Guyot *et al.* [12] detected a CDKN2A SNV (NM_000077, exon2, c.G442A, p.Ala148Thr) in a study which examined 30 MG series. The presence of such CDKN2A alterations was significantly associated with a Ki-67 labeling index > 7% (P=0.004). Another recent report [13] specified the overall prognostic role of the CDKN2A/B status in 528 MG cases, and observed that MGs carrying CDKN2A/B homozygous deletions showed a significantly worse outcome and more rapid evolution. Based on the mentioned records the strong association between homozygous deletion of CDKN2A/B mutations and aggressive clinical prognosis resulted in a significant revision in the WHO CNS5 criteria [14,15]. CDKN2A/B alterations with TERT promoter mutations, have been comprised in grade III MGs classification [15]. (Table 1)

Somatic mutations

KLF4 (Krueppel Like Factor 4) Mutations

KLF is a transcriptional regulator which retains stemness and observed to play both oncogenic and tumor suppressor roles in diverse types of cancer, such as gastric, bladder, and esophageal cancers [46]. KLF loss of function has been implicated in colon cancer, whereas its overexpression has been found to lead to decreased tumorigenicity of colon cancer cells *in vivo* [47]. In MG cases it is one of two genes revealed to be mutated in whole-exome sequencing of 16 secreting MGs [44]. In anaplastic MGs its overexpression has been linked with tumor suppressor proteins increased expression such as p53, p21, and BAX, suggesting a possible anti-tumor role in higher grade tumors [45]. Repeated KLF4 (c.1225A>C, $KLF4^{K409Q}$) mutations are possible candidate drivers of WHO grade I MGs [24]. KLF4 mutant MGs appears in approximately 28% of NF2 wild-types [48], which are commonly found in the non-middle anterior and central skull base [25]. According to WHO CNS5, KLF4/TRAF7 mutations represent the driver change in secretory MGs and are able to serve as alternative criterium, apart from secretory granula, to recognize that subtype [15]. (Table 1)

TRAF7 (Tumor Necrosis Factor Receptor-Associated Factor 7) Mutations

TRAF 7 encodes for a ubiquitin E3 ligase and is the second most often mutated gene in MGs [24]. It is responsible for catalyzing a diversity of ubiquitination reactions, such as that of p53 tumor suppressor gene, which has been observed to promote tumor progression in hepatocellular cancer whereas stabilizing p53's anti-tumoral effects in breast cancer [49]. TRAF7, is localized on chromosome 16p13, encodes for a protein which has been associated with configuration of Janus kinase and Mitogen-Activated Protein Kinase (MAPK) signaling pathways, inflammation and apoptosis induction [38,50]. Those mutations often result in structural alterations in the protein WD40 [38,50]. The mutation is also observed in 25% of MGs, which appear in 50% of NF2 wild-types [24,29].

Tumors which carry mutations in TRAF7 are frequently localized at the sphenoid wing and floor of the middle fossa [51]. TRAF7 mutations mainly appear in WHO grade I MGs, while only 4% of high-grade MG samples carry mutations in that gene [51]. At the present time it is regarded that the co-existence of TRAF7 and PIK3CA mutations shows long-term recurrence of skull base MGs [38,52]. TRAF and KLF4 mutations frequently co-occur in secretory MGs [44], with 40% of TRAF7-mutated MGs harboring a KLF4 mutation [50]. TRAF7 is also one of the following genes, KLF4, AKT1, and SMO, which is possible to be mutated in non-NF2 mutated MGs localized at the skull base [24]. TRAF7 mutations are also firmly associated with hyperostosis and often observed in spheno-orbital MGs [53]. TRAF7 mutations seem to be mutually exclusive of NF2 mutations but often have an associated mutation in AKT1 or KLF4 [24,26,38,44]. In a multi-center retrospective clinical study with 469 cases was observed that MGs harboring TRAF7 mutation were more susceptible to recur within two years [29]. (Table 1)

TERT promoter (TERTp) Mutations

Telomeres are conserved, repetitive (TTAGGG) DNA-protein clusters which are added to the ends of chromosomes by telomerase to prevent DNA damage and maintain replicative potential. Telomere attrition during DNA replication results in genomic instability which can lead to tumorigenesis [58]. TERT encodes for telomerase reserve transcriptase, which constitute a telomerase catalytic subunit which in turn promotes cell immortalization *via* telomere elongation [59]. TERTp mutations were primarily observed in melanoma cases and subsequently found in intracranial tumors, such as low-grade gliomas, oligodendroglioma, gliosarcoma multi-form, and medulloblastoma [58]. Those mutations also appear specifically in the the hotspot regions C228T and C250T, and have been found in 6.5% to 11% of MGs. It has been assessed the TERTp for mutations in the mentioned locations in a sample of 252 MG cases, and mutations were detected in 16 MG samples (6.35%) [56]. In another [55] was analyzed the sequence of the TERTp in 73 tumor cases and found a high occurrence of TERTp mutations in MG cases undergoing malignant histological progression.

Mutations in the chr5:1,295,228 (C228T) and chr5:1,295,250 (C250T) locations of the TERT promoter have been linked with uncontrolled proliferation in various types of cancer [57,58], and recently in MGs which exhibit histological malignant transformation [55]. TERTp mutations are more commonly detected in higher grade MGs, with mutations found in 1.7%, 5.7% and 20% of 2007 WHO classification grade I, II, and III MGs, respectively. TERTp mutations are comprised in the 2021 WHO classification of grade III MGs [15]. The results of a similar article [54] showed that TERTp alterations were observed in WHO I to III MGs. (Table 1)

AKT1 and PIK3CA mutations in the phosphatidylinositol-3 kinase (PI3K) pathway

AKT 1 encodes for AKT1 kinase, which is implicated in the regulation of cell growth and survival through a diversity of pathways [60]. AKT1 mutations result in PI3K/AKT signaling pathway activation [61]. Clark *et al.* applied exome sequencing to 300 MG cases, and AKT1mutations were found in 13% of those cases [24], whereas among skull base MGs, AKT1 mutations were recorded at a higher frequency of 30% [62]. In the same report was also observed that mutations in AKT1 activated mTOR and ERK1/2 signaling pathways [62]. AKT inhibitors have been found to downregulate osteoglycin (OGN) expression, an oncogene implicated in MG growth, *in vitro,* and to stabilize meningotheliomatous MG development in the lung of a patient with multiple intra- and extra-cranial tumors [63,64].

PIK3CA encodes for a phosphatidylinositol 3-kinase (PI3K) catalytic subunit which has been implicated in various human cancers [66]. PI3K signaling pathway abnormal activation consists one of the most common events in human cancer development and is involved in the control of cell growth, survival and metabolism from exogenous growth stimuli [67]. The PI3K pathway relevance in MGs is highlighted by the existence of various

PI3K mutations [37]. $AKT1^{E17K}$, $PIK3CA^{E545K}$, and $PIK3CA^{H1047R}$ are the most frequent mutation positions in PI3K pathway-related driver genes [24,68]. MGs which carry $AKT\ 1^{E17K}$ mutation are almost exclusively found in WHO grade I tumors and incline to have meningothelial and transitional histo-pathological morphology [69]. In addition, $AKT1^{E17K}$ mutant tumors are more commonly localized in anterior and middle fossa skull base [37,56,65,69]. The mentioned mutation has been recorded in 7% to 12% of sporadic MGs, resulting in abnormal activation of AKT1 and contributing to the tumor cells proliferation [37,56,65,68]. PIK3CA is mutated in approximately 4% to 7% of MG cases [24], whereas PIK3CA mutations are mutually exclusive of NF2, SMO, and AKT1 and in a small number of cases co-occur with TRAF7 or KLF4 mutations [24]. $PIK3CA^{H1047R}$ and $PIK3CA^{E545K}$ mutations, which have been revealed in PIK3CA, constitutively phosphorylate and activate AKT1 [38]. PIK3CA mutations are estimated to appear in 7% of non-NF2 mutated MGs and inclined to be mutually exclusive with the mentioned mutations in AKT1 and SMO [38]. In another study assessed 55 MG samples, PIK3 CA mutations were revealed in two patients who showed atypical and anaplastic MGs, respectively [119]. PI3K variations have also been observed to co-occur with TRAF7 mutations, with these tumors indicating lower levels of chromosomal instability and clinical trends to emerge in the skull base [38]. (Table 1)

RNA polymerase II subunit A (POLR2A) Mutations

POLR2A, is the RNA polymerase II catalytic subunit, is involved in the transcription of all protein-coding genes in eukaryotic cells, and it has been recognized in approximately 6% of grade I MGs. The repeated somatic hotspot mutations concern $POLR2A^{L438H}$ and $POLR2A^{Q403K}$ [26], has been found to harbor mutations which describe a distinctive subset of MGs which lack the mentioned mutations commonly observed in other MGs.

MGs which carry mutations in POLR2A were exclusively benign with distinct meningothelial histology and were more probably to come from the tuberculum sellae [58]. POLR2A mutant MGs are exclusively WHO grade I tumors which have been found in anterior skull base tumors, especially tuberculum sellae, and seem to have a meningothelial histopathological morphology [24,26].

It has been recorded [29], a longer time to recurrence in MGs with POLR2A mutation compared with that in other MG types. However, in that study the tumor samples with POLR2A mutation only composed 4.9% of the total samples, and tumor recurrence was found in 13% of cases. In another clinical report with 269 MG cases tumor recurrence was recorded in 29.4% of those patients harboring POLR2A mutation (5/17) with a mean time to recurrence of 45.6 months [120]. In addition, POLR2A mutation was a risk factor for the tumor recurrence in WHO grade I skull base MGs [84,85]. (Table 1)

BRCA1-associated protein (BAP1) mutations

BAP1 is a tumor suppressor gene which encodes a de-ubiquitylating enzyme and has been recognized in a rare aggressive MGs subset with rhabdoid morphology [70]. BAP1 mutation in those tumors was an

important event for the separation of rhabdoid-appearing MGs into aggressive and less-aggressive tumors [71]. Recognition of a germline BAP1 mutation requires increased vigilance in cancer surveillance in individuals who carry that mutation [72]. Moreover, BAP1 protein expression loss displays early MG recurrence [71]. (Table 1)

Duchenne Muscular Dystrophy (DMD) Mutations

The DMD gene encodes the protein dystrophin, and germline mutations in that gene are driving factors of the disease [73]. DMD inactivation plays an essential role in the growth and progression of diverse solid tumors [74,75]. In a retrospective clinical study by Juratli *et al.*, [76], with 169 high-grade tumor samples from 53 cases, DMD gene inactivation was observed to be associated with shorter Overall Survival (OS) and Progression-Free Survival (PFS), and it was considered to be an independent risk factor for poor prognosis in those patients. In another similar study [120**]** was found that DMD aberration was detected to be enhanced in MGs with NF2 mutations, and DMD was among the most differentially up-regulated genes in NF2 mutant compared with NF2 wild-type cases. However, the DMD specific role in those tumors remains to be determined. (Table 1)

Polybromo-1 (PBRM1) mutations

Polybromo-1 (PBRM1) is a tumor suppressor gene encoding the BAF180 subunit of the SWI/SNF complex and is implicated in the tumor cell proliferation and migration regulation [77]. PBRM1 gene alterations were recorded in 40% of papillary renal carcinomas, renal clear-cell carcinomas, and bladder ones [78]. Recent research [79], stated the presence of high-frequency mutations in PBRM1 in papillary MGs, WHO grade III, with updated criteria of WHO CNS5. That observation was confirmed in a follow-up study with 950 cases, which observed that 87.5% of PBRM1 mutations appeared in WHO grade II and III MGs [30]. The mentioned observations have contributed to understand the molecular bio-signatures of high-grade MGs. (Table 1)

Epigenetic alterations in meningioma

H3K27me3 alterations

Histones are highly sustained proteins constituted of core proteins, which together with DNA compose nucleosomes. Histone modification reversibly suppresses or expedites gene transcription and also affects other processes, such as DNA repair, stem cell formation, replication, and cell state alterations. The Lys 27 trimethylation on histone 3 (H3K27me3) is a chromatin modification which is firmly associated with gene repression and plays a critical role in the intracranial tumor's growth and progression [80,81]. A distinct asscіation between H3K27me3 loss and MG recurrence has been observed in multiple retrospective clinical studies [82,83]. Katz *et al.* [83], observed that H3K27me3 loss increased the clinical recurrence risk of MGs and demonstrated a discrete effect on the clinical prognosis of WHO grade I and II cases, based on the results from 232 MG reports. In another retrospective survey in 181 tumor samples, H3K27me3 immuno-histochemical staining of paraffin sections and clinical variable analysis were examined, and the out-comes showed that H3K27me3 loss increased the risk of tumor recurrence in WHO grade I and II tumors [82]. (Table 1)

TIMP3 Methylation

DNA methylation is one of the prematurely detected and most well-analyzed epigenetic regulatory mechanism. That process is catalyzed by the DNA methyltransferase family and implicates the transfer of a methyl group to carbon 5′ of cytosine in genomic CpG di-nucleotides. DNA methylation is responsible for controlling gene expression by inducing modifications in chromatin structure, DNA configuration, DNA stability, and DNA-protein interactions [86].

TIMP3, CDKN2A, and TP73 hypermethylation appears in 10% of MGs [87]. The hyper-methylation of TIMP3 is responsible for a down-regulation in transcription product and leads to loss of tumor suppressor activity [88]. Hyper-methylated TIMP3 has been observed in 40% to 60% of high-grade tumors, and those cases frequently show rapid recurrence after treatment [87,88]. Moreover, because TIMP3 is localized in chromosome 22 (22q12), almost all MG individuals with TIMP3 hyper-methylation are escorted by allelic loss of 22q [88]. In another multi-center retrospective clinical study [89], the authors found that MGs could be divided into two definite subtypes liked with PFS through clustering analysis of global DNA methylation data. In a similar way [90] MGs divided into two major classes and six subtypes based on clustering data of DNA methylation, and those subtypes showed distinctive genomic elements and clinical manifestations. (Table 1)

TP73 promoter (TP73p) Methylation

The human TP73 gene which is localized on the short arm of chromosome 1 (1p36.32), is a TP53 homologous family gene with a sequence greatly similar to that of TP53. TP73 is duplicated into two major functional subunits, TAp73, and DNp73. TAp73 is a tumor suppressor gene which plays an essential role in suppressing p53-mutated tumors, whereas DNp73 acts as a tumor promoter. P53 is broadly mutated in tumors, however its mutation rate in primary tumors is only 0.6% [90].

The principal pathways which are responsible for the abnormal expression of p73 are allelic loss and TP73 promoter hyper-methylation. Diverse studies have confirmed that methylation of TP73p was present in 70% to 80% of high-grade MGs, however that event is not frequent in WHO grade I tumors [91], suggesting a certain specificity of TP73p methylation in high-grade MGs. In another study [92], the authors stated that TP73p methylation represented 20% of MGs and was not linked with tumor grade. Similarly, another report [87], showed that the TP73p methylation rates in WHO grade I to III MGs were 13%, 19% and 33%, respectively. However, the two mentioned reports com-prised only three WHO grade III tumor samples and used different methylation primer sequences for polymerase chain reaction detection, which may result in biases in their outcomes [87,92]. (Table 1)

Genes responsible for Meningiomas	Mutation type
NF2	Function Loss [11,17-30]
KLF4	KLF4 K409 Q missense (Somatic mutations) [15,24,25,44-48]
TRAF7	WD40 domain mutation (Somatic mutations) [24,26,38,49-53]
TERT	TERT promoter chr: 1,295,228 (C228T) and chr: 1,295,250 (C250T) regional mutations (Somatic mutations) [15,54-59]
SWI/SNF	Frameshift deletion [41,48]
SMO/SUFU	Function Gain [29-40]
AKT1	Function Gain (Somatic mutations) [60-65]
CDKN2A/B	Function Loss mutation (Homozygous deletions) [11-16]
PIK3CA	Function Gain (Somatic mutations) [66-69]
POLR2A	Function Gain mutation (Somatic mutations) [24,26,58]
SMARCE1/SMARCB1	Somatic mutations [6,41-44]

BAP1	Somatic mutations [70-72]
DMD	Somatic mutations [73-76,119]
PBRM1	Somatic mutations [30,77-79]
Cytogenic alterations in Meningiomas	**Alteration type (Copy Number Alterations)**
22q	Deletion (Loss) [5-7]
14q (14q11.2)	Deletion (Loss) [8,110,112-117]
1p (1p33-1p34,1p-36)	Deletion (Loss) [109-111]
10q	Deletion (Loss) [31,32, 112]
18q (18q22)	Deletion (Loss) [9,10, 112]
6q	Deletion (Loss) [112]
17q	Deletion (Loss) [112]
20q	Deletion (Loss) [112]
Epigenetic alterations in Meningiomas	
H3K27me3	Trimethylation [80-85]
TIMP3	Methylation [9,86-89]
TP73 promoter	Methylation [87,90-92]

Table 1: Molecular alterations detected in Meningiomas

Medulloblastoma

Medulloblastoma (MB) is a primary brain tumor which affects children and young adults. It is the most frequent malignant brain tumor in pediatric population children [121], as already mentioned.

MB cell of origin

It has been histologically evidenced that Wingless signaling activated (WNT), and Sonic-Hedgehog signaling activated (SHH)MBs rise from different cell types. MBs come from cells which are associated with some extent to cerebellar granule-neuron-precursor (CGNP) development and that some MB cells preserve aboriginal elements equivalent to those of the embryonic brain precursors. Consequently, it is possible that the obtainment of CGNP identity is an essential determinant of progenitor cells' ability to form Hedgehog-induced MBs [122].

WNT MB cell of origin

WNT MBs origin is considered controversial [123], as decades ago was suggested that these tumors come from a hypothesized CNS precursor cell known as medulloblast. However, that cell has never been revealed, and it was proposed that the tumor [124] belongs to a group of histologically similar CNS tumors, which called primitive neuro-ectodermal tumors (PNETs). Recent data showed that, the cells of origin for the SHH sub-group are the granule-neuron progenitors, whereas for Groups 3 and 4, early rhombic lip was regarded the common source of origin [125]. MBs differentiate along glial and neuronal pathways *in situ*, suggesting that these tumors are come from primitive, pluripotent, neuro-epithelial stem cells, observation which is supported by studies of PNET cell lines which demonstrate expression of specific, developmentally regulated proteins in PNETs [126]. It has been detected that MBs express zic, a gene normally expressed only in the External Granule cell Layer (EGL) of the developing cerebellum and its byproducts, suggesting that MB comes from EGL precursor cells. Based on the rapid proliferative ability of EGL precursors and the pattern of gene expression seen, EGL cells and their byproducts appear the most possibly origin of the tumor. Other cerebellar cells, such as glial cells, Purkinje cells, or basket neurons, are not likely to be origin cells for MB. Murine models of human MB have shown that other stem cells in the cerebellum may are responsible for MB development [127].

A model of MB has been raised using the GFAP promoter to drive RecA recombinase expression, resulting in RB1 tissue-specific inactivation [128]. The study also showed that, cells expressing GFAP were presented in the developing cerebellum, although the vast majority of EGL precursors did not express GFAP. Based on the rapid proliferative ability of EGL precursors and the pattern of gene expression seen, EGL cells and their byproducts appear the most possibly origin of the tumor.

SHH MB cell of origin

SHH MB is similar to the granule cell precursor (GCP) origin in terms of transcription process, which is consistent with previous researches demonstrating SHH MBs rise from the GCPs at the external granular layer [129]. Single-cell RNA-sequence also revealed additional heterogeneity within SHH MB, which consists of various different phases of GCP development, suggesting a model in which SHH MB develops in a manner consistent with the GCP prelacy [130]. Conditional Patched knockout mice using Math1-cre/Ptcc/c which eclectically produce a two-hit inactivation of Ptc in GCPs evolve MB suggesting that GCPs are able to be responsible as the origin cell for SHH MB [129].

Group 3/4 MB cell of origin

Single-cell analysis comes from the developing mouse cerebellum suggested that group 3/4 MB rises from an earlier stem cells population and unipolar brush cell origin, respectively [131]. However, single-cell analyses using the developing human and mouse cerebellum outline the differences in developmental standards where human rhombic lip (RL) insists longer than mouse RL, making questions regarding previous perceptions from mouse developing cerebellum. Human RL spreads into the RLvz and the RLsvz by a vascular plexus at 11 post-conception weeks [131]. The same article using the developing human cerebellum data, revealed that group 3/4MB cells were most similar to the RLsvz except for a group 3γ subtype part which showed enrichment for the earlier RLvz [131]. CBFA2T2 and CBFA2T3 were greatly expressed in the RLsvz but neither RLvz nor unipolar brush cell, demonstrating that the CBFA complex defines cell fate. Smith *et al.* using multi-omics data outlined that group 3/4 MB matches the molecular signatures including the gene expression standard with progenitor cells in the RLsvz as well [125]. The mentioned reports suggested that deferred differentiation of progenitor cells in RL led the development of group 3/4 MBs.

MB Molecular Classification

Several studies reported that MBs concern at least four explicit molecular subgroups, Wingless signaling activated (WNT), Sonic-Hedgehog signaling activated (SHH), Group 3, and Group 4, mainly based on transcriptome profiles and a few known genetic alterations [132,133]. Afterwards, for the first time in 2016, molecular subgroups of MBs were comprised into the WHO's MB classification [134]. The WNT and SHH groups were revealed and named based on the signaling pathways that were detected to be activated in WNT MBs and SHH MBs, respectively. The WNT subgroup represents approximately 10% [135] of all MBs, whereas the SHH subgroup is most frequent in infants and young adults, representing 25% of all MBs [133]. Group 3 and Group 4 account for approximately 65% of MB cases and are characterized by great

heterogeneity in clinical phenotypes and survival rates [136]. According to the most recent edition of CNS tumor classification (CNS 5), in 2021, MBs were divided into "molecularly" and "histologically" determined, suggesting the diverse biology of the tumor [137].

Cavalli *et al.,* [138] categorized four subgroups further into 12 subtypes based on DNA methylation and gene expression profiles, whereas Northcott et al. [139] classified group 3/4 MB into eight subtypes based on DNA methylation profiling. Although the MB sub-type classification is still in the provisional stage, it is widely accepted that each subtype is a distinct entity supported by a subtype-specific manner of recurrent genetic events. In the updated WHO CNS tumors classification, Group 3 and Group 4 are combined into one, known as non-WNT/non-SHH MB. It is a very large class, which contains the majority of pediatric MB patients [137]. Another classification by Smith *et al.* divides MBs into seven subtypes and highlights that the only group which remains intact concerns the WNT-MB class. Recently, a unified lineage of origin for both Groups 3 and 4 within the human fetal RLsvz was determined which explain the underlying molecular signatures, biological and clinical sheathing, and location of diagnosis that these two groups share [125].

The WNT MB subgroup

The WNT is a family of growth factor receptors which are implicated in embryogenesis and in cell-cell control mechanisms [140]. WNT/β-catenin signaling pathway is a highly conserved pathway which regulates key cellular functions comprising differentiation, proliferation, genetic stability, migration, apoptosis and stem cell renewal. Abnormalities in this pathway are involved in diverse cancers such as colon cancer, adrenocortical tumor, melanoma, breast cancer, high grade glioma and MB [140]. WNT-signaling path-way mutations are responsible for its principal activation [141]. The WNT subgroup is the least frequent among the four MB molecular subgroups, representing approximately 10-15% of the cases. It can appear at any age; however, it is most frequently observed in children 6-12 years of age with slight female predominance [139,141,142]. The great majority of WNT tumors are of classic histology, whereas only rare cases are of large cell/anaplastic (LCA) variant and are never nodular desmoplastic (ND) [142]. The dorsal midbrain lower RL progenitor cells have been evidenced to be the cells of origin in WNT tumors. That observation is supported by the fact that anatomically, WNT MB often appears in a central location, commonly abutting the brainstem and protruding through the Luschka foramen [133,138,140]. A rate 85-90% of WNT MB cases harbor mutations in CTNNB1, the gene encoding for the protein β-catenin.

The vast majority of WNT MB cases (85-90%) have a mutation in exon 3 of CTNNB1 according to genomic analyses [143]. As a result, β-catenin is stabilized, resulting in WNT pathway constant activation [144]. Mutant β-catenin protein is resistant to degradation, resulting in its accumulation in the nucleus [144]. Whole-genome sequencing has detected recurrent somatic mutations in WNT MB except CTNNB1 gene. The most dominant among those genes are TP53, DDX3X, SMARCA4, and KMT2D. Those gene mutations have been observed in approximately 50%, 26%,15% and 12% respectively, and they are not exclusive to WNT MB. The most conventional genetic mutation in the WNT subgroup is also DDX3X, which is an RNA binding protein of the DEAD-box family. That protein functions as a tumor suppressor in MB which regulates hindbrain development [145]. The DDX3X mutations have been detected in 11% of SHH MB and 3% of group 3 MB, whereas SMARCA4 is a SWI/SNF pathway critical ingredient, which plays an important role in the development of multiple cancers such as ovarian, renal and liver cancer, melanoma, and other tumors. The TP53 mutations have been revealed in 14% of SHH MB, and KMT2D is presented in 13% of SHH MB and 4% of group 3 MB. Those genes encode proteins which interact with nuclear β-catenin and remodel chromatin, suggesting that cooperative mutations are involved in the development of this tumor subtype [138,139,141].

Monosomy 6 is observed in 80-85% of WNT MB, which is strongly related to a WNT pathway immuno-histochemical profile. It is a hallmark chromosomal abnormality of WNT MB and is rarely found in other subgroups although a minority of tumors preserve two copies of the chromosome [146]. The WNT MB subgroup is most accurately diagnosed by sequencing exon 3 of CTNNB, gene expression or DNA methylation profiling [147]. A valid and more accessible way to diagnose this subgroup is the nuclear β-catenin accumulation, monosomy 6 (whole chromosome loss) by FISH [147,148]. Basing solely on the positivity of immuno-histochemistry for β-catenin may result in an incorrect diagnosis of a WNT subgroup due to motley nuclear accumulation in some WNT cases. That concerns also monosomy 6, which can be occasionally revealed in other subgroups [147,148].

Controversial data exists regarding the MBs' subtypes within the WNT group, as some studies have reported evidence for at least two distinct subgroups, whereas other have reported only one [138,149]. Because of the confusion regarding the above mentioned subclassification, many subdivisions have been suggested. Some groups use testing of gene-expression patterns with DNA-methylation arrays. A recent and modern approach is the similarity-network-fusion (SFN) procedure, which makes networks of combined data [138]. The WNT-MB was molecularly divided into two subgroups: WNT-α (70%) and WNT-β (30%) [138]. The first subgroup appears mainly in children with ubiquitous monosomy 6, in contrast to the second group in which most of the patients are adults and chromosome 6 is diploid [138]. However, that classification is still controversial, as the 5th edition of WHO classification does not accept subtypes for WNT MB [137,138]. (Table 2)

The SHH-MB Group

SHH MBs are the most frequent group in infants, representing 25% of all MB cases. Commonly, it is located in cerebellar hemispheres, however it can also be observed in the midline. It is characterized by mutations or CNAs of SHH-pathway genes. Robinson *et al.,* suggested that the infant-SHH group should be split into SHH-I and SHH-II, as it is possible that the first one is enriched in SUFU aberrations and chromosome 2 gain [150,151]. It has also been suggested the sub-classification of the SHH group into α, β, γ, and δ subgroups [138,141]. Among those SHHα, affects children and adolescents, and corresponds to SHH-3 in the 5th edition of the WHO classification, SHHβ, affects infants, and corresponds to SHH-1, SHHγ, which also affects infants, and corresponds to SHH-2, and SHHδ, which affects adults, and corresponds to SHH-4 [137]. Except the clinical and transcriptional differences, each SHH subtype has distinct gene mutations standards, where SHHα and δ have a higher mutation burden than SHHβ and γ [152].

Some of the driver mutations are restricted to a certain subtype, as, whereas mutations in TP53 and ELP1 are generally restricted to the SHHα subtype, TERT promoter mutation is exclusive to the SHHδ subtype [138,138,153,154]. The SHHα subtype with TP53 mutation usually carries U1 snRNA mutation [153] whereas ELP1 mutation is enriched in the remaining SHHα cases without TP53 mutation [154]. Based on the study, infant SHH-I and SHH-II correspond to SHH-β and SHH-γ, respectively. SHHα can be of the LCA (Large Cell/Anaplastic) or ND (Desmoplastic/Nodular) subtype. It has been observed to be enriched with MYCN, GLI2, and YAP1 amplifications, and also TP53 mutations and CNAs (9q,10q, and 17p loss) [138,155].

The SHH signaling pathway seems to play an essential role in cerebellar development [188]. The receptor for SHH is a membrane-associated protein containing 12 transmembrane domains [156-158], known as patched (PTCH1). The effector molecule, smoothened (SMO) is associated with PTCH in the membrane. PTCH's function is to inhibit signaling by SMO. Binding of SHH to PTCH releases the mentioned inhibition, resulting in the intracellular components activation of the pathway [138].

SHH MB exhibits SHH signaling pathway activation. SHH is one of the secreted proteins which belongs to the Hedgehog family which in turn is well conserved during evolution and plays an essential role as cell differentiation induction signals in the CNS growth process [159]. The most commonly altered genes within the SHH signaling pathway concern PTCH1 (44%-45%), SMO (11%-14%), SUFU (8%-11%), and GLI2 (8%-11%), resulting in the GLI2 consecutive activation, which is the downstream target of the SHH signal [139,152]. In the canonical SHH signaling pathway, the glycoprotein SHH binds and inactivates the receptor PTCH1, which inhibits the G protein-coupled trans-membrane protein SMO. PTCH1 inhibition allows SMO to initiate an intracellular signaling cascade which results in the GLI2 translocation into the nucleus, leading to the transcriptional activation of target genes [160].

Suppressor of fused (SUFU) is a negative intracellular regulator, which suppresses GLI activity by controlling the production, transport, and function of GLI proteins [161]. Consequently, PTCH1 and SUFU mutations are identified as loss-of-function mutations. On the contrary, SMO and GLI2 alterations are detected as gain-of-function mutation or focal amplification, respectively. Implication of altered genes in the SHH signaling pathway in the growth of MB has been revealed in mouse models where mice with heterozygous deletion of PTCH1 or active form of SMO develop MB, indicating that mutations in the SHH signaling pathway are responsible for MB tumorigenesis [162]. (Table 2)

Mutations in the cAMP-dependent pathway

A recent analysis of mutations in SHH MB cases revealed recurrent mutations in GNAS and PRKAR1A, which are implicated in the cAMP-dependent pathway [152]. Mutations in GNAS and PRKAR1A were observed in 4.4% and 2.0% of SHH MBs, respectively, as they resulted in GLI2 activity, which is the key mediator of the SHH signaling pathway for MB pathogenesis. GNAS encodes the heterotrimeric Gs protein α subunit (Gαs) and regulates survival, cell development, and motility [163]. GNAS is mutated in a wide spectrum of tumors such as growth hormone-producing pituitary tumors, corticotropin-independent Cushing syndrome, and thyroid adenomas [164]. GNAS mutations in the endocrine glands tumors activate hotspot mutations clustering around R201 and Q227, whereas, GNAS mutations in SHH MB inactivate mutations clustering in the GTP/ GDP binding site of Gαs, resulting in inhibition of GTP binding and increase GDP release [165]. GTPase activity inhibition in Gαs reduces cAMP concentration, leading to the protein kinase A (PKA) inactivation which is a SHH signaling pathway negative regulator [166]. GNAS knockout mice developed SHH MB with 100% penetrance, supporting the role of GNAS as a driver in SHH MB tumorigenesis [167]. PRKAR1A encodes the PKA regulatory subunit type I-alpha. Mutations in PRKAR1A are localized within the binding region of the cAMP-binding domain and reduce cAMP sensitivity, leading to impairment of the PKA activation [168]. Mutations in GNAS and PRKAR1A were observed in a mutually exclusive manner. Moreover, individuals with alterations in GNAS or PRKAR1A scarcely harbor any alterations in the canonical SHH signaling pathway such as PTCH1, SMO, SUFU, and GLI2, further indicating their imperative role in SHH MB tumorigenesis [152]. Altogether, the cAMP-dependent pathway inactivation in SHH MB is the alternative mechanism deteriorating the SHH signaling pathway control. (Table 2)

Mutation in RNA-processing machinery

In recent years, sequencing technology efforts have revealed highly recurrent mutations in U1 snRNA and ELP1genes, both of which are implicated in RNA processing [153,154,169]. U1 snRNA has various functions such as splice-site recognition. ELP1 encodes the largest subunit of the elongator complex which is required for tRNA modifications. Except U1 snRNA and ELP1, genes associated with the RNA-processing machinery concern U11 snRNA and XPO1 are recurrently affected in SHH MB, indicating that aberrant RNA processing is one of the key elements of SHH MB pathogenesis [139,152,153]. (Table 2)

U1 and U11 snRNA mutations

U1 snRNA is an essential component of the spliceosome and is involved in genesplicing. U1 snRNA mutation is the most frequent single-nucleotide variant in MB and is restricted to the SHH subgroup [153,169]. The mutation is a hotspot mutation with A to G substitution at the third nucleotide (g.3A > G), which forms part of the 5′ splice-site recognition sequence [170]. In SHHα cases, U1 snRNA mutation is generally escorted by TP53 mutation, whereas mutations in PTCH1, SMO, and SUFU are usually absent [139,153]. As U1 snRNA binds to 5′ splice site by base-paring, mutant U1 snRNA recognizes non-canonical 5′ splice sites, leading to excess of 5′ cryptic splicing.

The cryptic splicing in U1 mutant SHH MB is revealed in more than 1,000 genes including several oncogenes (GLI2, CCND2) and tumor suppressor genes (PTCH1, PAX5), suggesting that cryptic alternative splicing induced by U1 snRNA mutation functions as a driver in SHH MB. Recently was recorded additional novel functions of U1 snRNA other than splice-site recognition. U1 snRNA suppresses premature cleavage and polyadenylation by base pairing to pre-mRNA [171]. Moreover, it is recorded that U1 snRNA determines the localization of RNAs to chromatin [172]. U11 sn RNA is also repeatedly mutated in SHH MB generally along with U1 snRNA mutation, although rarely (3.7% in SHHMB). (Table 2)

ELP1 mutations

ELP1 is a subunit of the elongator complex, which is essential for tRNA modification to uridine at the wobble position (U34), which is the first anticodon of tRNA and recognizes the third nucleotide in a codon [173,174]. As a result, loss-of-function of ELP1 harms elongator-dependent tRNA modification at the wobble position. The uredines chemical modification at the wobble position is crucial for proper mRNA decoding, and its absence affects codon translation rates [174,175]. Consequently, mutant ELP1 tumors have a significant codon usage bias, where AA ending codons are inefficiently recognized but AG-ending codons are efficiently recognized [146,154]. The alteration in codon usage leads to the significant up-regulation of gene sets related to RNA splicing, amino acid activation, and activation of the endoplasmic reticulum stress pathway in SHH MB with ELP1 mutation [154,176]. Mutations in ELP1, formerly known as IKBKAP, were detected in 14% of pediatric SHH MBs as the most conventional germline mutation [154].

The ELP1 mutations have been revealed as a loss-of-function mutations predominantly in the U1 wild-type SHHα subtype and are usually escorted by somatic PTCH1 mutations. ELP1 mutation is mutually exclusive with mutations in TP53. Therefore, cases with ELP 1 mutation have a relatively good prognosis. (Table 2)

XPO1 mutations

Mutations in XPO1 have been detected in 8.5% of U1 mutant SHH MBs [152]. Those mutations are commonly observed in primary mediastinal diffuse large B cell lymphoma and classical Hodgkin's lymphoma as a hotspot mutation (p.E571K) [177]. On the contrary to the mentioned hematological cancers, the majority of XPO1 mutations in SHHMB are truncated mutations. XPO1 is a nuclear export protein which carries proteins and RNAs, and snRNAs, from the nucleus to the cytoplasm, indicating that RNA exportation and maturation are deranged in XPO1 mutant SHH MB. Accumulating evidence showed that post-transcriptional aberration is another key component in SHH MB [178]. (Table 2)

The Group 3/4 MB

Recent studies reported that group 3/4 MBs rise from progenitor cells of the ventricular RL (RLvz) or the subventricular RL (RLsvz), suggesting

that the progenitor cell differentiation stage could reflect group 3/4 MB subtypes [125,131]. In group 3/4 MBs some of the genetic events are in a subtype-specific manner. MYC amplification is enriched in group 3γ, which has the poorest prognosis [138]. OTX2 amplification and GFI1 activation or GFI1B gene expression by enhancer capturing are frequent in group 3β [125,138]. MYCN amplification is commonly revealed in group 4α [138]. Group 4β, which is regarded the purest subtype consisting of only group 4 MB frequently, has potential duplication of SNCAIP, which is responsible for PRDM6 activation [138]. The subtype-specific manner of recurrent genetic events supports the idea that each subtype is a distinct entity with its own genetic features. (Table 2)

Genetic alterations in the CBFA complex

A recent large-scale sequencing report detected somatic mutation of CBFA2T2 in 3.1% of group 4 MBs [131]. CBFA2T2 is a transcriptional co-repressor which connects transcription factors and epigenetic modifiers, and interacts with the PRDM proteins SET and PR domain including PRDM6. Moreover, focal chromosome 16q24 deletions, where another CBFA family gene is localized, CBFA2T3, are enriched in conditions without CBFA2T2 or PRDM6 alterations. Protein interaction assays *in vitro* showed that CBFA 2T2 interacts with KDM6A, which is a known drive gene. Alterations which affect CBFA2T2, CBFA2T3, PRDM6, and KDM6A are almost mutually exclusive, giving support for their role as cancer drivers [131]. (Table 2)

Genetic predisposition in MB and association between congenital cancer Syndromes and MB

MB has been observed in conjunction with several rare disorders, including Gorlin syndrome (associated with mutations in SUFU and PTCH1), Li-Fraumeni syndrome (TP53), Fanconi anemia (BRCA2) and APC-associated polyposis conditions [179]. In a recent report, Waszak *et al.* analyzed blood samples for germline mutations from 1,022 MB cases (673 from previous retrospective cohorts and 349 from prospective studies) and matched them with 800 available tumor samples for 110 cancer predisposition genes. Damaging germline mutations were observed in 11% of the retrospective cohort and the outcomes were replicated in the prospective study. The most relevant genes revealed were APC, BRCA2, PALB2, PTCH1, SUFU and TP5 [94] (Table 2). The prevalence of the above-mentioned genes was 6% overall and 20% in SHH-MB cases. Three study also showed that G3 and G4 subgroups were rarely related to germline mutations and the absence of biallelic germline mutations in mismatch repair genes (only one case harbored heterozygous germline mutation in MSH6 gene) [94]. The authors suggested that patients with WNT and SHH-MBs were most frequently related to a genetic predisposition, and 50% of the identified cases had no relevant family history. MBs may appear in combination with two distinct inherited cancer syndromes, Turcot and Gorlin syndrome. Nevoid Basal Cell Carcinoma Syndrome (NBCCS), or Gorlin syndrome or basal cell nevus syndrome, is an autosomal dominant disorder [180]. Affected individuals develop multiple basal cell carcinomas, and other pathological conditions, whereas at least 40 MB cases have been described in patients with that syndrome, indicating that about 3% of Gorlin patients develop MB [181].

The gene for Gorlin syndrome has been designated to chromosome 9q22.3 [95]. The results of two researches detected loss of genetic markers mapped to 9q in MB. The first examined 16 patients with 12 microsatellite markers mapping between 9q13 and 9q34 [96]. Two tumors (12.5%) showed LOH with microsatellite markers in that location. The second study examined 20 cases, 17 with sporadic tumors and 3 with NBCCS, which were searched with seven microsatellite markers mapped to 9q22.3 to 9q31 [182]. Three of the 17 sporadic tumors also showed LOH on 9q. It is remarkable that all three of the tumors from NBCCS cases were identified as desmoplastic MBs. The other three tumors with LOH on 9q were among six desmoplastic tumors in the sporadic group. Consequently, all of the tumors with LOH on 9q were desmoplastic, increasing the possibility that an NBCCS gene mutation is implicated in the development of this MB subclass. The gene at 9q22.3which is responsible for NBCCS has been identified as the PTCH gene, the human homolog of the Drosophila patched gene [157,158]. The Drosophila gene encodes a protein with 12 putative trans-membrane domains, and it may function as a receptor or transporter [183]. That protein has an essential role in the mentioned fly development, and a similar role in humans may explain the congenital abnormalities associated with NBCCS.

Turcot syndrome is a hereditary disease in which the patients develop multiple colonic polyps and a brain tumor, either glioblastoma multiforme or MB [184]. Mutation in adenomatous polyposis coli (APC), which is a germline mutation, is also related to WNT MBs. A study by Hamilton *et al.* showed mutations in the APC gene which were revealed in the group of patients with Turcot syndrome who developed MB [97]. The relative risk for appearing a MB in Turcot syndrome patients and an APC gene mutation is 92 times than in the general population. The role of APC as a tumor suppressor protein is determined by the control of the free β-catenin levels in the cytoplasm by APC. Under normal circumstances, β-catenin free levels are low, as binding of β-catenin by APC isolates β-catenin and targets the protein for degradation. APC acts as a key regulator in a complex developmental signaling pathway, as in the cytoplasm is connected with at least seven proteins, such as β-catenin, b-TrCP, axin1 and 2, glycogen synthase kinase 3b (GSK-3b), the B6 subunit of the PP2A phosphatase, and hDLG [185,186]. APC only binds β-catenin in case β-catenin is hyper-phosphorylated. β-Catenin is phosphorylated by GSK-3b, a serine/threonine kinase. After APC inactivation caused by mutation, (e.g., in colon carcinoma), β-catenin cytoplasmic levels increase. Free β-catenin is connected with Tcf family members [187]. After the mentioned connection, the complex moves to the nucleus and up-regulates the genes expression which increase the rate of cell division, either by stimulating cell proliferation or by inhibiting apoptosis.

Other Growth Factor Pathways in MB

It has also been investigated [100,188,189] the erbB family members expression in MB, and was shown that erbB2 and 4 were frequently expressed together in the tumor. To be more specific erbB4, but not erbB2, was expressed in the developing cerebellum. ErbB2 and erbB4 expression was associated with simultaneous expression of neuregulin 1-a, suggesting the possibility of an autocrine loop in tumors with expression of the mentioned proteins. Indeed, erbB2/erbB4 dimerization was revealed in tumors. It has also been shown that novel erbB4 splice variants were observed frequently in MB [100]. (Table 2) IGF-1R activation has also been identified in MB cell lines [190]. Autophosphorylation of this receptor and c-fos expression induction in the presence of exogenous IGF-1 have been found, indicating a functional receptor. Tumor development could be inhibited by an anti-IGF-1R antibody which interferes with ligand binding [101]. (Table 2)

Epigenetics in MB

Besides the genetic alterations, epigenetic deregulation appears in 30-40% of MB cases [102,135]. Epigenetics implicates alterations in the gene function which are mitotically and/or meiotically heritable and that do not concern alterations in the individual's DNA sequence. This is affected through DNA methylation, histone modifications, chromatin remodeling, microRNAs and LncRNAs [102]. As mentioned, childhood MBs harbor multiple genetic mutations resulting in tumorigenesis. However, there are subtypes, mainly G3 and G4, which have no stated mutations, suggesting the role of epigenetic dysregulation [102].

Hypermethylation of 5′-Cphosphate-G-3′ (CpG) dense promotors (CDKN2A, H1C1 and RASSF1) results in the silencing of tumor suppressor genes, such as PTCH1, SFRP family and ZIC2[102,191]. Somatic mutations and copy number abnormalities in HDACs, demethylases, histone lysine methyl-transferases, and also members of the poly-comb transcriptional repressor complex (PRC2 and PRC1) have been detected across all four MB subgroups. Abnormal histone

methylation at H3K27 and H3K4 have been observed in G3 and G4 MB. Mutations in KDM family members are among the most frequent re-current events in G4 MB. miRNAs and long noncoding RNAs (LncRNAs) have been found to play a role in MB. mi-RNAs can either be suppressed (miR-124) or overexpressed (miR-17~192). The LncRNAs regulate the gene expression, nuclear structure, and post-transcriptional processing [102,192]. (Table 2)

Karyotypic Abnormalities in MB

Only one karyotypic abnormality has been detected to be typical of MB, the isochromosome 17q, which is present in approximately 50% of tumors [98]. The breakpoint has been localized to 17p11.2, but no tumor-specific gene rearrangement has been revealed. No specific tumor-suppressor gene that can be implicated in the MB development has been detected on chromosome 17p. Especially, no alteration in p53 has been observed with more than 100 MBs investigated until now. The breakpoint for the rearrangement has been mapped to 17p11.2 [99]. Other less conventional karyotypic abnormalities, such as LOH on chromosome 9q, have been found in approximately 20% of MBs. In addition, it is important to mention that the loss of 9q in those tumors has been associated with the desmoplastic subtype [182]. (Table 2)

Medulloblastoma types	Molecular alterations
WNT subgroup	-WNT/β-catenin signaling pathway [139,140], CTNNB1[142], TP53, DDX3X, SMARCA4, KMT2D [137,138,140,143,144] Mutations -HDACs, histone lysine methyl-transferases, PRC2, PRC1 somatic mutations and CNAs [102,191] -Monosomy 6 [145-147]
SHH-MB subgroup	-Sonic-Hedgehog (SHH) signaling pathway genes (CNAs) 136,137,140,149-151], TP53, ELP1 [137,138,152,153,175], U1snRNA/U11snRNA [152,168,169]], SMO, PTCH1, SUFU [138,151], GLI2 [137,138,151,154], GNAS, PRKAR1A [151, 162, 164,166], XPO1 [151,176,177] mutations -MYCN, YAP1 [137,154], IGF-1R [101,189] amplifications -HDACs, histone lysine methyl-transferases, PRC2, PRC1 somatic mutations and CNAs [102,191]
3/4-MB subgroup	-MYCN, OXT [124,137] amplification, GFI1/GFI1B [124,137] Activation -CBFA2T2/CBFA2T3 [130], PRDM6, KDM6A [130] somatic Mutation, -APC, BRCA2, PALB2, PTCH1, SUFU, TP5 [94] somatic Mutations -ErbB aberrant signaling pathway [100,187,188] -HDACs, histone lysine methyl-transferases, PRC2, PRC1 somatic mutations and CNAs [102,191] -H3K27 and H3K4 abnormal histone methylation [102,191] -Isochromosome 17q (most frequently) [98,99,181]

Table 2: Molecular alterations in Medulloblastomas

Conclusions

MGs are the most frequent primary intracranial tumor and among the most well-investigated intracranial neoplasms. Although the previous classification system by the WHO was used to predict its recurrence risk and prognosis, advances in molecular biology profiling contributed to the development of diverse new classification systems utilizing DNA -level rather than histopathological observations. MG diagnosis and treatment remain a clinical challenge affected by evolutions regarding its natural history, pathogenesis signaling pathways, and treatment modalities. Recent advances in genetics and epigenetics have led to further molecular classification, and identification of molecular determinants of treatment response in MG cases. MB is a complicated group of four diseases characterized by genomic, biologic and clinical diversity even within the same group. A great deal of observations regarding the genetic alterations leading to that pediatric brain neoplasm has been mentioned. Neoplasm subgroups with alterations in genes which play an essential role in CNS development have been identified and murine models based on some of those observations have been established. However, further research is needed to clarify the nature of alterations are responsible for uncontrolled cell proliferation in a majority of those neoplasms.

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