Review

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Comparative Analysis of the Embryonal Brain Tumors Based on Their Molecular Features

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Pediatric brain tumors currently show the highest incidence among solid childhood malignancies and, together with leukemia, are the leading cause of death from cancer in childhood. Embryonal brain tumors are the most common and frequent type of childhood brain cancer and are usually characterized by an extremely aggressive course of the disease with the worst outcomes in most cases. There is an urgent need for specific refined molecular diagnostics, which would help to develop personalized treatment. In the present review paper, the latest molecular characteristics of various classified forms of embryonal brain tumors were analyzed in detail. Overexpression of the *MYC* and *MYCN* genes is characteristic of many embryonal brain tumors, leading to enhanced cell proliferation and disturbances in the cell cycle. The functioning of the SWI2/SNF2 chromatin remodeling complex are distorted in such malignancies as well. Noteworthy, LIN28 and MYC discussed here are involved in the induction of pluripotency. We have to mention that molecular mechanisms underlying the development of embryonal brain tumors of the central nervous system (CNS) are still not well understood. Thus, it is important to uncover such mechanisms with the aim to provide a better prognosis of the course of disease and to create personalized therapy.

Keywords: embryonal brain tumors; molecular features; classification

Introduction

Embryonal brain tumors are the most common solid tumors in the pediatric population. Such tumors are characterized by an extremely aggressive course of disease and a high risk of adverse outcomes in most cases. According to the data provided by the Central Brain Tumor Registry of the United States, tumors of the central nervous system (CNS), along with leukemias, dominate among young patients [1] with the highest average incidence rate, especially for CNS tumors (5.83 per 100,000 compared with, for example, 0.79 for bone tumors or 1.05 for soft tissue tumors) [2]. These numbers are quite similar in many countries; in Ukraine, the incidence rate of embryonal CNS tumors is 4–5 cases in 100,000 pediatric population [3]. In Northern England, the incidence rate of these tumors is up to 1.5-fold lower than in the United States [4].

Embryonal brain tumors are quite heterogeneous and include different subtypes of diverse origin and epidemiology, reflected in multiple clinical features and, consequently, treatment approaches [5]. In 2007 the World Health Organization (WHO) classified CNS tumors primarily on the basis of their cell type origin, histological features, and degrees of differentiation [6]. Given the scientific and medical knowledge and the diagnostic tools at the time, such classification was entirely appropriate. Since 2007, new experimental results on genetic abnormalities and molecular features of embryonal brain tumors were obtained, leading to a large array of novel and supplemented data, which necessitated reconsidering the classification of embryonal tumors of CNS [7,8].

Hence, in 2016, the WHO provided an updated nosology where all known embryonal brain tumors were re-classified on the basis of their genetic and molecular features. According to the 2016 classification, embryonal brain tumors include medulloblastoma, atypical teratoid/rhabdoid tumors, and tumors with multilayered rosettes (with subgroups included in each category) (Fig. 1) [9–11].

WHO's 2021 classification contains no significant changes in the definition of embryonal brain tumor nosology compared with the classification from 2016. However, all tumors were now distributed into only two groups—medulloblastomas and primitive neuroectodermal CNS tumors (Fig. 1) [12]. We wanted to characterize in detail each group of embryonal brain tumors and emphasize the specific molecular features and functioning corresponding signaling pathways in malignant cells.

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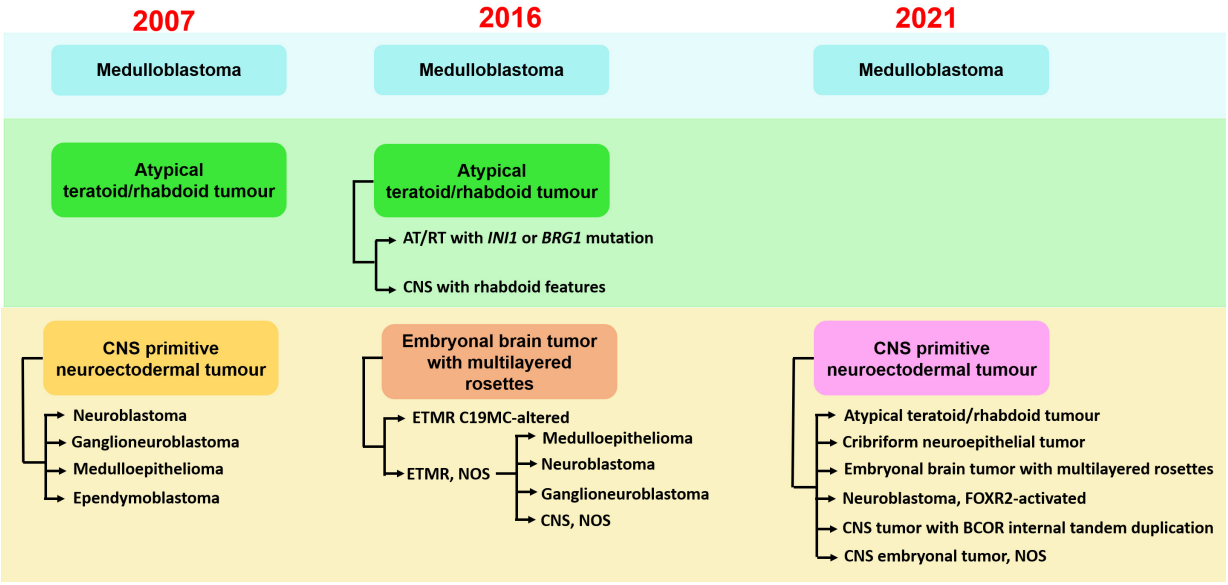

Fig. 1. A comparative analysis of the World Health Organization (WHO) 2007, 2016, and 2021 classification of central nervous system (CNS) embryonal tumors. ETMR, Embryonal tumor with multilayered rosettes; AT/RT, atypical teratoid/rhabdoid tumor; NOS, not otherwise specified; *C19MC*, *the chromosome 19 miRNA cluster*; *FOXR2*, *Forkhead box R2*; *BCOR*, *BCL-6 corepressor*. (Drawn with MS Office 365 PowerPoint, Microsoft, Redmond, WA, USA, the same below.)

Medulloblastomas

Medulloblastoma is the most frequent form of solid CNS tumor in pediatric oncology [13]. Medulloblastoma is detected predominantly in infants and early childhood; up to 70% of cases are reported in children under 10, while the vast majority of cases are detected in children 5 to 7 years old [1]. Medulloblastoma among adults is rare; the incidence rate is almost 10-fold lower than among the pediatric population. Interestingly, the incidence rate of medulloblastoma in boys is almost twice as high as in girls [14]. The prognosis for patients' survival is varied and depends on many factors, such as the immunohistological variant of medulloblastoma, presence of metastasis, general condition of the patient, presence of concomitant disorders, especially endocrinopathies, etc. The mortality rate in the first years after diagnosis of medulloblastoma is approximately 15%. With the appropriate treatment strategy, the five-year survival rate of the patients could be much higher [15]. However, the 15 years of survival data obtained in England from 2001 to 2015 showed that patient survival gradually decreased with time to approximately 60% for the ten-year period, from about 75% in the 5-year period and nearly 91% in the first year of observation [16].

Medulloblastoma is localized in the cranial cavity, named posterior cranial fossa, and arises from precursor cells of the developing cerebellum or, rather, from cells of its external granule layer. On histological slides, medulloblastoma appears as a dense cluster of mostly undifferentiated cells with scanty cytoplasm and huge hyperchromatic nuclei; thus, these cells are sometimes called "medulloblasts" for their morphological similarity to other normal blast-type cells [17,18]. The high proliferative potential of medulloblastoma, evidenced by the majority of present cells being in the mitotic phase of the cell cycle, together with subsequent cell dissemination and metastasis formation, has led to the conclusion that medulloblastoma is an extremely malignant tumor. The main path for metastasizing of medulloblastoma is through cerebrospinal fluid, and metastases are usually detected within a cerebellum surface and along the spinal cord [19,20].

An in-depth study of genomic alterations, expression profiles of transcription factors, the state of molecular pathways, etc., revealed significant differences between medulloblastomas cases that became the main reasons for the division of medulloblastomas into four molecular groups: (i) Wingless/Int-1 (WNT)-activated, (ii) sonic hedgehog (SHH)-activated, (iii) group 3, and (iv) group 4 [10,11].

WNT-Activated Medulloblastomas

Topologically, WNT-activated medulloblastomas (WNT-MBs) are located centrally in the middle part of the cerebellum and often can spread toward the cerebellar peduncle or brainstem [21]. WNT-MB is not found among infants and is uncommon in adults (no more than about 10%–15% of all cases) but is prevalent in children 10–12, with equal gender distribution [22,23]. WNT-MB has low metastatic potential; metastases were detected in less than 9% of cases, and relapse was rare. Histological slides of WNT-MB show the classic morphology, and given the previous data, this is associated with the favorable prognosis of almost 95% survival rates [24,25].

The canonical WNT/β-catenin signaling pathway is highly active during embryogenesis, including neurogenesis. Since the WNT signaling controls the most critical events in development, such as cell proliferation and migration, appropriate formation of body axial patterning, cell differentiation and fate specification, etc., any disturbances that cause changes in normal signaling could lead to imbalance and, eventually, to cancerogenesis [26,27].

Typically, activation of the canonical WNT signaling pathways is initiated by joining WNT family proteins to the membrane receptors and the Frizzled family on the target cells. The binding of WNT with an extracellular cysteine-rich domain of Frizzled causes the conformation changes in the latter, which allows recruiting of the cytoplasmic protein Dishevelled toward the cell membrane. Interaction between these proteins occurs by joining the DEP domain and the C-terminal region of Dishevelled with two domains in the third cytoplasmic loop and a part of the C-terminal tail of Frizzled. Because of the Dishevelled–Frizzled binding, phosphorylation of the lipoprotein receptor-related protein (LRP)-5/6 is induced. The latter is a co-receptor and is needed for the WNT signaling transduction. pLRP-5/6 further recruits the proteins to the cell membrane, forming a β-catenin destruction complex, namely Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 beta (GSK3β), and cyclin-dependent kinase inhibitor proteins (CKIs). This complex becomes immobilized, which makes it impossible to interact with β-catenin for its phosphorylation, ubiquitination by beta-transducin repeat containing E3 ubiquitin protein ligase (BTRC), and final degradation. Thus, activation of the WNT signaling pathway results in β-catenin accumulation and its translocation into the nucleus, where this protein functions as a coactivator for T cell factor (TCF), which induces transcription of a set of target genes, encoding proteins that can activate cell growth and proliferation [28–31].

The WNT-MBs account for approximately 10% of all MBs and are characterized by somatic mutation in exon 3 of *catenin beta 1* (*CTNNB1*) gene encoding for β-catenin. This mutation is detected in over 90% of WNT-MB cases and used as a routine immunohistochemistry marker for differential diagnosis (Fig. 2A) [11,17,32]. Mutation in exon 3 of the *CTNNB1* gene leads to conformation changes in the N-terminal domain, where binding sites for glycogen synthase kinase 3 beta (GSK3β) and cyclin-dependent kinase inhibitor (CKI) are located. This prevents phosphorylation of β-catenin and contributes to its accumulation [33,34].

The accumulation of β-catenin observed in a given MB group is due to *CTNNB1*-gene mutation, which alters GSK3β/CKI binding sites. In other words, such β-catenin accumulation is not linked with activation of the WNT signaling pathway. Perhaps there could be other reasons unrelated to the action of the WNT ligands. These relevant questions are still unanswered, which makes them important to pursue in future studies.

According to the reported research data, except for *CTNNB1*, several other elements of the canonical WNT signaling pathway could be altered in medulloblastomas. In approximately 10% of the WNT-MB cases, cancerous cells carry the unmutated *CTNNB1* gene. They harbor *adenomatous polyposis coli* (*APC*) germline pathogenic variants and are usually associated with colorectal cancers (known as the "Turcot syndrome") or with other pathologies, such as malignant hepatoblastomas, pilomatricomas, epidermoid cysts, osteomas, etc. (Fig. 2A) [35]. Historically, alterations in *APC* were discovered in colorectal cancers. Moreover, it was shown that a significant proportion of mutations occur within the domain responsible for β-catenin binding and downregulation [36,37]. These data may indicate a functional relationship between the presence of *APC* mutations and activity levels of the WNT signaling pathway in WNT-MBs. However, the knowledge of this relationship is limited. Recently, it was shown that WNT-MBs with mutated *APC* are characterized by high expression levels of the anaplastic lymphoma kinase (ALK). Moreover, a strong correlation between the WNT-MB phenotype and *ALK* expression on both mRNA and protein levels was also found. On the basis of these observations, this marker could be used for differential diagnosis of WNT-MBs bearing *APC* mutations [38,39] in addition to a favorable prognosis for patients with high *ALK* expression.

The *tumor protein p53* (*TP53*) gene could also be mutated in WNT-MBs; however, this alteration is unrelated to the clinical prognosis [40]. Mutations in the *DEAD-box RNA helicase 3X* (*DDX3X*) gene are frequently observed in many types of cancers, including SHH-activated medulloblastomas (SHH-MB) and WNT-MB, with frequency in the latter of about 50% (Fig. 2A) [41]. *DDX3X* encodes the RNA helicase DDX3X involved in initiating the mRNA translation process by directly binding to its 5′UTRs. *DDX3X* is the tumor suppressor gene and is usually mutated in MBs. When a DDX3X inhibitor was applied to MB cell lines, a cell proliferation rate was decreased, at the expense of the reduced TCF activity, leading to G_1 arrest and apoptosis induction [42].

The *SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4* (*SMARCA4*) gene is mutated in approximately 26% of WNT-MBs. Similarly, to *DDX3X* and *TP53*, the mutated *SMARCA4* is not the key feature of this subtype of MBs, as other molecular MB groups show such alterations (Fig. 2B) [41]. *SMARCA4* encodes the SMARCA4 protein (also known as BRG1), an ATP-dependent unit of a supramolecular complex for chromatin remodeling (SWI2/SNF2). Because SMARCA4 could be involved in the regulation of gene expression and it is often mutated in different cancer types, this gene is considered the tumor suppression gene [43,44].

Finally, WNT-MBs could be associated with the chromosome 6 monosomy (Fig. 2B). Notably, about 70% of

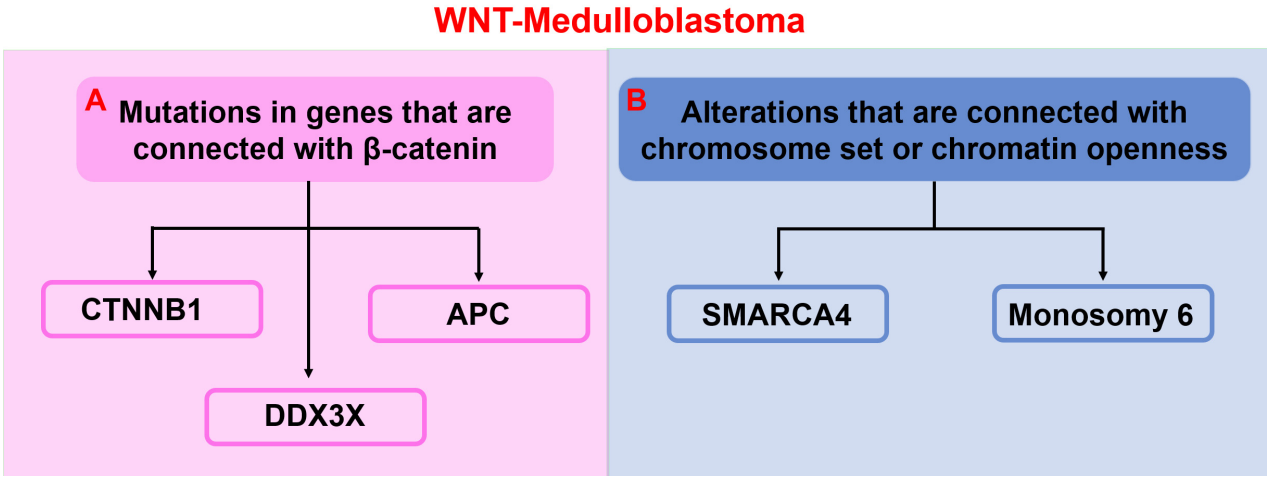

Fig. 2. A Schematic Summary of Common Genetic Alterations in WNT-activated medulloblastomas (WNT-MBs). (A) Mutations in genes that are connected with the *CTNNB1* gene. (B) Alteration in genes, associated with the chromatin structure. *CTNNB1*, *catenin beta 1*; *APC*, *adenomatous polyposis coli*; *DDX3X*, *DEAD-box RNA helicase 3X*; *SMARCA4*, *SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4*.

WNT-MBs, characterized by the chromosome 6 monosomy, were observed mainly in child patients. This form of tumor is associated with a favorable outcome and is designated as WNT-α. The resting 30% of WNT-MBs carry a diploid set of chromosome 6, a type of tumor typical for adult patients [45].

SHH-Activated Medulloblastomas

Sonic hedgehog (SHH)-activated medulloblastomas (SHH-MBs) are characterized by the presence of the germline or somatic mutations in components of the SHH signaling pathway, leading to its hyperactivation and accounting for approximately 30% of all detected MBs [46]. SHH-MBs are located in the cerebellar hemispheres, unlike other subtypes of MBs with a middle arrangement. SHH-MBs originate from precursors of granule cells of a cerebellum external layer [47].

A characteristic feature of SHH-MBs is that they have the highest incidence rate in children under 4 years of age and in young adults over 16 [41]. In most cases, SHH-MBs are desmoplastic/nodular (almost 50%). They could also be classic or large cell/anaplastic (LCA), which makes this group the most heterogeneous by morphology. It should be noted that the LCA phenotype is predominantly observed in SHH-MBs with the mutated *TP53* gene (discussed below) and is diagnosed mainly in children 4 to 17 years old [17,48]. The clinical prognosis for survival of the SHH-MBs is approximately 60%–80%, depending on genetic abnormalities and a morphological type [22,41]. The most optimistic prognosis for 10-year survival of up to 84% is observed in infants with desmoplastic/nodular tumors [49].

The sonic hedgehog (SHH) signaling pathway is initiated through the interaction between the SHH ligand and the transmembrane receptor Patched-1 (PTCH1). The palmitoylated N-terminus of SHH is incorporated in a cavity formed by the two extracellular domains (ECD-I and ECD-II) PTCH1 [50]. When PTCH1 is unligated, this protein inhibits the function of a transmembrane G-protein-coupled receptor Smoothened (SMO, SMOH), the key regulator of activation of the glioma-associated oncogene (GLI) transcription factors (GLI1, GLI2, GLI3) and results in the expression of SHH target genes. It is known that cholesterol activates SMO via binding with an extracellular cysteine-rich receptor domain. Moreover, activated PTCH1 is involved in cholesterol transport, but the exact mechanism of this is still unknown [51]. Activation of SMO leads to inhibition of the protein kinases PKA and GSK3β. These kinases, when activated, phosphorylate the main inhibitor of GLI transcription factors, suppressor of fused homolog (SUFU). Such negative regulation promotes SUFU dephosphorylation and proteasomal degradation with a simultaneous release of GLI factors, which translocate to the nucleus and activate the transcription of the target genes [52,53].

Depending on the patients' age, various mutations are detected in approximately 30% of SHH-MBs. In particular, the most noted germline mutations in infants' cancerous cells are in *PTCH1* (Gorlin syndrome), *SUFU*, and *TP53* (Li-Fraumeni syndrome). Most adult somatic mutations are detected in genes such as *PTCH1*, *SMO*, *telomerase reverse transcriptase* (*TERT*), and *isocitrate dehydrogenase 1* (*IDH1*) (Fig. 3A,B) [54]. There are limited data on the functional alterations in encoded proteins due to the listed mutations. However, it is known that the *PTCH1* and *SUFU* mutations incapacitate the ordinary functioning of the PTCH1/SUFU protein, while the mutated SMO protein becomes more activated [11,41,55].

The Li-Fraumeni is a hereditary syndrome with an autosomal dominant inheritance related to *TP53* mutations

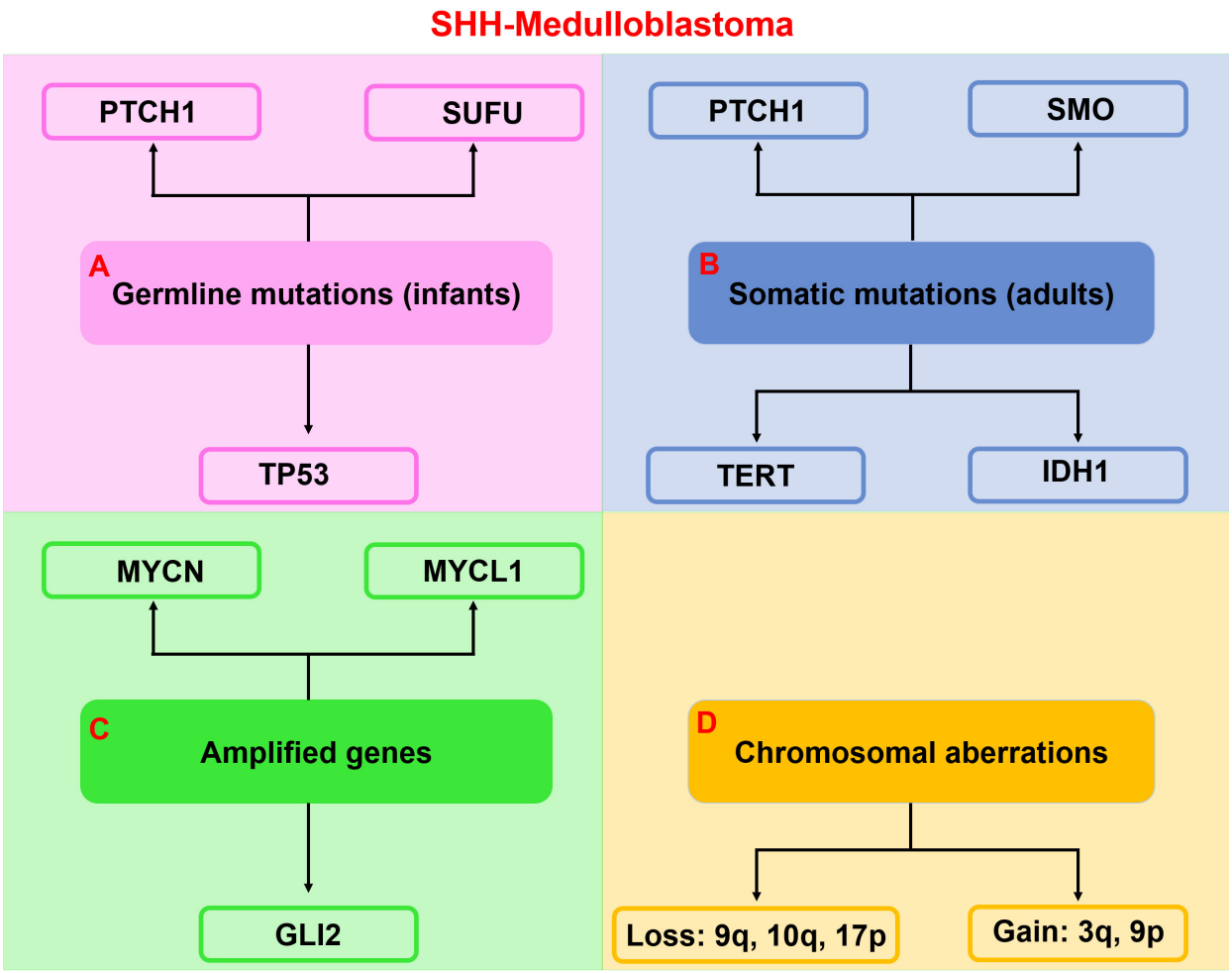

Fig. 3. A Schematic Summary of the Common Genetic Alterations in SHH-MBs. (A) Germline mutations. (B) Amplified genes. (C) Somatic mutations. (D) Chromosomal aberrations. *SHH*, *sonic hedgehog*; *PTCH1*, *Patched-1*; *SUFU*, *suppressor of fused homolog*; *TP53*, *tumor protein p53*; *SMO*, *Smoothened*; *TERT*, *telomerase reverse transcriptase*; *IDH1*, *isocitrate dehydrogenase 1*; *MYCL*, *MYCL proto-oncogene, bHLH transcription factor*; *GLI2*, *glioma-associated oncogene (GLI) family zinc finger 2*.

and associated with an increased rate of cancer development. Almost in all tumor cases in patients with Li-Fraumeni syndrome, the germline missense mutations in the TP53 DNA–binding domain were found in the cancerous cells [56]. Since TP53 generally functions as the tumor suppressor, such mutations reduce its ability to function correctly as the transcription factor and provide antitumor protection. Among all cases of SHH-MBs bearing the *TP53* mutant, approximately 60% are germline mutations [40]. The 5-year overall survival of SHH-MBs patients carrying wild-type *TP53* is 75%–80%, much higher than in patients with tumors with abnormal *TP53* (about 40%) [17,40].

The mutated *TP53* is not the only alteration within SHH-MBs. Detected mutations in the *TP53* gene are commonly associated with general chromothripsis and massive chromosome rearrangements, such as amplification of the *MYCN* and *GLI2* genes (Fig. 3C) [57]. It was shown that if *GLI1* and *GLI2* are expressed among the *GLI* family of transcription factors coordinating expression of SHH target genes *(GLI1-3)*, the overall SHH-MB patients survival rate is up to 2 times lower than with *GLI1*/*GLI2*-negative SHH-MBs cases. Moreover, the knockdown of *GLI2* in experimental MB cell lines inhibited the cell viability and proliferation rate, probably due to G_0 arrest [58]. These data may partially explain why exactly *GLI2* is more often amplified.

Amplification or at least upregulation of the *MYCN* gene, which encodes the N-Myc transcription factor, is a common feature of MBs and other types of brain tumors [59]. Noteworthy, both *MYCN* and *MYCL proto-oncogene, bHLH transcription factor* (*MYCL*) *1* (Fig. 3C) are amplified and highly expressed in SHH-MBs; however, only amplification of *MYCN* correlates with poor prognosis [23]. Moreover, the amplification of *MYCN* shows a strong associative connection with the LCA phenotype, another indicator of poor clinical prognosis [60].

On the basis of the existing molecular characteristics, methylation profile, and the character of clinical outcome, four SHH-MB subtypes were proposed: SHH-α (adoles-

cent with mutated *TP53* and amplification of *MYCN/CLI2*, 29% of cases), SHH-β (infants with high metastatic activity and extremely poor prognosis, 16% of cases), SHH-γ (infants with extensive nodularity and good prognosis, 21% of cases), and SHH-δ (adults with mutated TERT, 34% of cases) [45].

In addition, SHH-MBs could carry multiple chromosomal aberrations, namely frequently deleted regions in 9q, 10q, or 17p. These abnormalities are associated with the origin of gene mutations described earlier, such as *PITCH1*, *SUFU*, and *TP53*. There is frequent gain in such regions as 3q and 9p, in addition to chromosomal losses (Fig. 3D) [44,47].

The remaining MB cases (about 60%), with no established association with activation or inhibition of any specific signaling pathways, are grouped as non-WNT/non-SHH cases of MBs. Most commonly, these cases are classified as molecular groups 3 and 4, representing extremely aggressive cancers with poor prognosis. In such cases, patients show weak responses to treatment, and the extensive metastatic process is often noted at the time of diagnosis [27]. Another reason groups 3 and 4 are traditionally considered in tandem, despite differences in their molecular levels and clinical outcomes, is that they cannot be distinguished by immunohistochemical staining [11]. However, in a cohort of 300 MBs, it was shown that groups 3 and 4 cases could be separated using immunohistochemistry with specific antibodies against Natriuretic peptide receptor 3 (NPR3) and potassium voltage-gated channel subfamily A member 1 (KCNA1) [61]. Nevertheless, these data are not yet included in the new classification because they were not yet validated [41].

Group 3 Medulloblastomas

Group 3 of MB tumors (G3-MBs) are usually located in the middle part of the cerebellum, more specifically, in the midline filling of the fourth ventricle. They have also been found in the cerebellum hemispheres, but such cases are rare [41,47]. The origin of G3-MBs cells is still a matter of debate. According to some sources, malignant G3-MBs cells arise from cerebellar granule neuron precursor cells within an external granule cell layer [21]. However, a transcriptome analysis of the G3-MB cells showed no similarities with any cell types within normal cerebellum architecture [62].

G3-MBs are usually diagnosed in young children, with the peak incidence around the age of 3–5 and mostly among males [63]. In general, the G3-MBs subgroup accounts for approximately 20%–25% of all diagnosed MB cases. The clinical prognosis for G3-MB patients is extremely poor. The overall 5-year survival rate is about 40%–60%, and every second case is burdened by extensive metastases [41]. According to an alternative classification, G3-MBs are divided into the subgroup G3-MB-α (infants, high metastatic dissemination, better prognosis, 47% of cases), G3-MB-β (low metastatic dissemination, activation of growth factor independence (GFI), 25% of cases), and G3-MB-γ (amplification of *MYC*, poor prognosis, 28% of cases) [45].

A common characteristic of all non-WNT/non-SHH cases of MBs is the significant presence of different genetic and chromosomal aberrations. The key feature of G3-MBs is an amplification of the *MYC* gene, up to 20%, followed by aberrant mRNA transcription/protein translation, promoting pro-tumorigenic events (Fig. 4C) [64]. It was reported that in the majority of G3-MBs, *MYC* amplification is due to the fusion between the second exon of *MYC* and a gene of noncoding RNA *plasmacytoma variant translocation 1* (*PVT1*), also co-amplified in many types of cancer. It should be emphasized that PVT1 stabilizes MYC activity because the PVT1–MYC protein fusion prevents MYC phosphorylation and degradation [65]. Except for *MYC*, amplification of *MYCN* and *orthodentricle homeobox 2* (*OTX2*) are also observed in G3-MBs; however, it happens more rarely, only in 5% and 3% of cases, respectively (Fig. 4C) [64]. The abovementioned genes and the encoded proteins belong to the critical regulators of the embryonal development of the nervous system's structural elements. That is why the loss of their tight regulation is generally a negative prognostic factor [60,66]. In addition, *MYC* and *OTX2* can function synergistically and promote a protumorigenic effect.

In approximately 15% of G3-MBs, overexpression of the *growth factor independent 1 transcriptional repressor* (*GFI1*) or *growth factor independent 1B transcriptional repressor* (*GFI1B*) genes (as mutual exclusion), which coordinates the cell fate decisions during development (Fig. 4B), is observed. This upregulation occurs via rearrangements in the chromosomal structure; thus, *GFI1* or *GFI1B* become closely associated with several enhanced genes [64].

In 5% of G3-MBs, mutations in the *SMARCA4*, *kelch repeat and BTB domain containing 4* (*KBTBD4*), *CTD nuclear envelope phosphatase 1* (*CTDNEP1*), and *lysine methyltransferase 2D* (*KMT2D*) genes have been observed (Fig. 4A) [44]. *SMARCA4* encodes an element of the multiunit complex for chromatin remodeling, the SWI2/SNF2, and, as was discussed earlier (see the WNT-MB characteristics), it is an important regulator of mRNA expression [43]. *KBTBD4*-encoded protein is an E3 ubiquitin ligase adaptor. The indel mutations (a blend of insertion and deletion) in this protein influence its substrate recognition, which becomes unbalanced. For example, mutated KBTBD4 could promote the degradation of REST corepressor (CoREST), an important regulator of epigenetic programs (through interactions with histone deacetylases), thus, influencing the availability of genes for transcription [67]. One of the proteins mutated in G3-MBs is the CTDNEP1 phosphatase, which is involved in regulating the MYC function. In particular, the mutated CTDNEP1 could phosphorylate MYC on serine-62, thus promoting MYC stabilization. More-

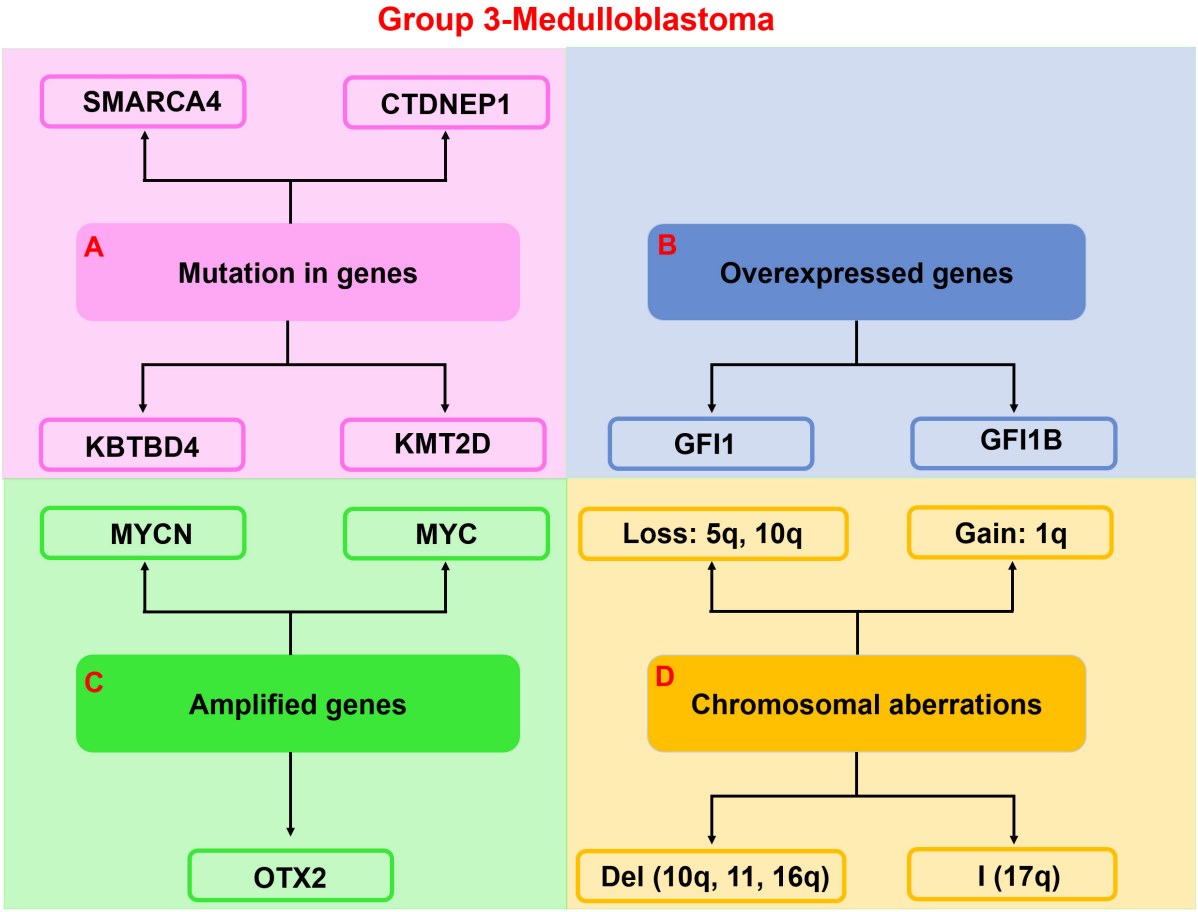

Fig. 4. A Summarizing Scheme of the Group 3 of MB tumors (G3-MBs) Common Genetic Alterations. (A) Gene mutations. (B) Gene overexpression. (C) Gene amplification. (D) Chromosome aberrations. *CTDNEP1*, *CTD nuclear envelope phosphatase 1*; *KBTBD4*, *kelch repeat and BTB domain containing 4*; *KMT2D*, *lysine methyltransferase 2D*; *GFI1*, *growth factor independent 1 transcriptional repressor*; *GFI1B*, *growth factor independent 1B transcriptional repressor*; *OTX2*, *orthodentricle homeobox 2*.

over, CTDNEP1 takes part in the promotion of cell proliferation by positively modulating the activity of topoisomerase II alpha (TOP2A) and checkpoint kinase (CHEK1). Histone methyltransferase KMT2D plays a crucial role in the regulation of gene transcription. Mutations in this gene lead to KMT2D loss of function, frequently occurring in many types of cancer, including MBs [68].

Except for gene mutations, extensive genomic instability is one of the key characteristics of G3-MBs, described by the presence of isochromosome 17q, gain in 1q, losses in 5q and 10q, or deletions in 10q, 11, and 16q (Fig. 4D) [41,69].

Group 4 Medulloblastomas

The location of Group 4 medulloblastomas (G4-MBs) is almost identical to that observed for G3-MBs; it is defined as the middle disposition in the cerebellum, filling the fourth ventricle [41,47]. It was suggested that G4-MBs originate in the unipolar brush cells located in the granular layer of the cerebellar cortex and confirmed by the transcriptome analyses [47,62].

G4-MBs are evenly distributed among patients of different ages; the median incidence is around age 9. G4-MBs account for almost one-half of all MB cases (about 45%) [41]. According to the data on gender distribution, G4-MBs are more frequently diagnosed in males [46]. The clinical prognosis for patients with G4-MBs is considered intermediate – the 5-year overall survival rate is about 60%–80%. The frequency of metastases in the G4-MB patients is slightly higher than in G3-MBs, about 40% [41].

A list of the most common gene aberrations that occur in G4-MBs includes amplification of *MYCN* and *cyclin dependent kinase 6* (*CDK6*), *duplication of synuclein alpha interacting protein* (*SNCAIP*), and *mutations in lysine demethylase 6A* (*KDM6A*), *zinc finger MYM-type containing 3* (*ZMYM3*), and *lysine methyltransferase 2C* (*KMT2C*) [63,64]. Mutation in the *MYCN* gene detected in G4-MBs is not unique to this type of cancer but is a typical alteration found in other MBs (Fig. 5C). The mutated *MYC* in SHH-MB and G3-MBs indicates a poor prognosis. In contrast, no association with the clinical prognosis in G4-MBs was observed [41,70]. Instead, amplification of *CDK6*, one of

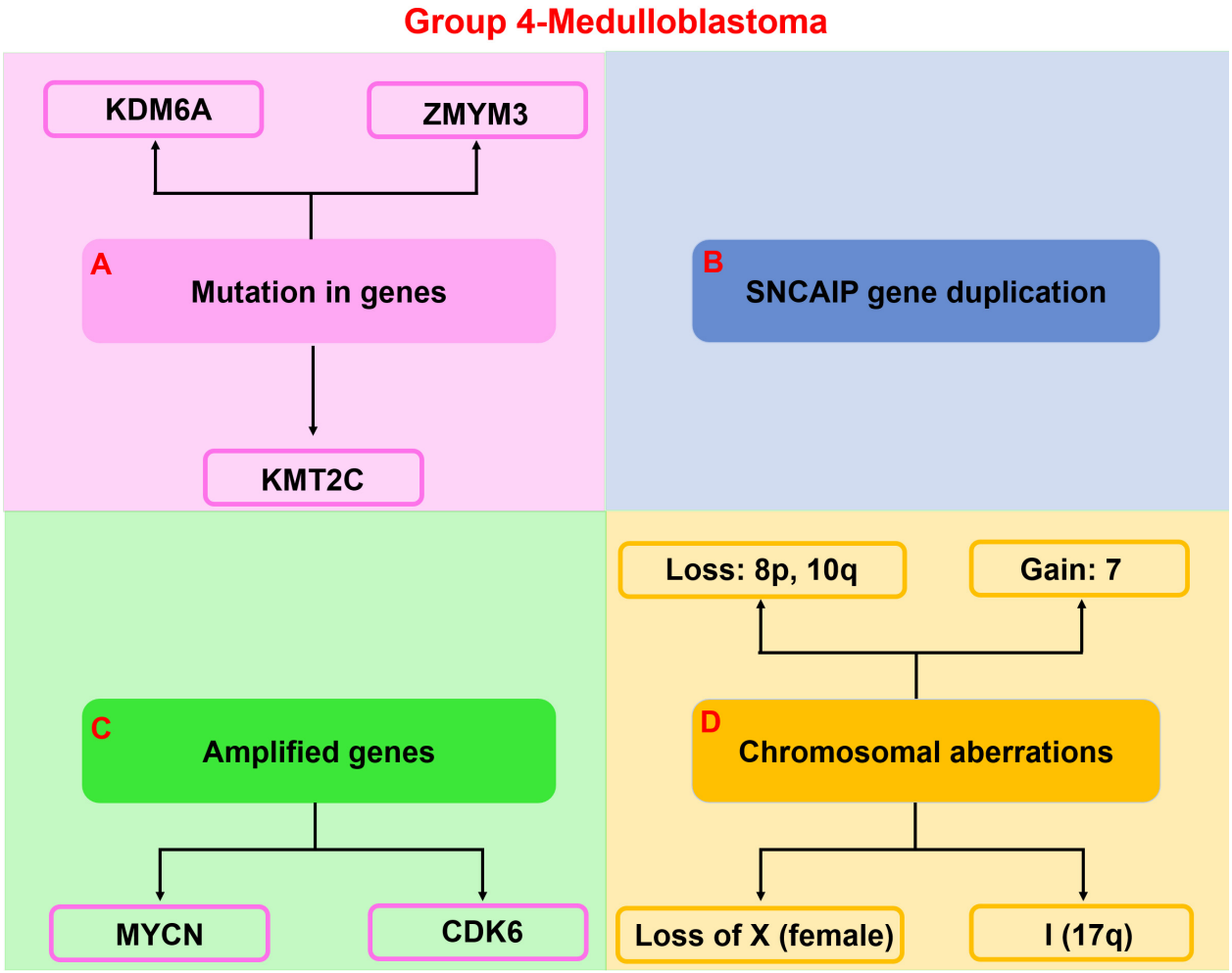

Fig. 5. A Summarizing Scheme of the Common Genetic Alterations in Group 4 medulloblastomas (G4-MBs). (A) Gene mutations. (B) Gene duplication. (C) Gene amplification. (D) Chromosomal aberrations. *KDM6A*, *lysine demethylase 6A*; *ZMYM3*, *zinc finger MYM-type containing 3*; *KMT2C*, *lysine methyltransferase 2C*; *SNCAIP*, *duplication of synuclein alpha interacting protein*; *CDK6*, *cyclin dependent kinase 6*.

the central regulators of the G_1-S transition and the cell proliferation rate, is common in G4-MBs and even proposed as a possible marker of this particular cancer subtype (Fig. 5C) [64,71].

Mutations in the histone demethylase KDM6A are observed in 13% of G4-MB cases, causing the inactivation of its function and resulting in an unbalanced transcription activity (Fig. 5A) [72]. The ZMYM3 and KMT2C proteins are also linked to regulating the chromatin modification process, including gene accessibility or involvement in the DNA damage response (Fig. 5A) [64]. No accurate information is available about the role of SNCAIP in the G4-MB development and progression, except that the *SNCAIP* gene is duplicated. However, considering that this protein contains many docking domains and thus could provide a wide range of protein–protein interactions, the presence of mutations in a SNCAIP structure could be related to the functions of yet undiscovered proto-oncogenes (Fig. 5B) [44,73].

Analogous to other MBs groups, G4-MBs cases were divided further into three subgroups based on molecular features: G4-MBs-α with presence of mutations in *MYC* (30% of cases), G4-MBs-β with duplication of *SNCAIP* (33% of cases), and G4-MBs-γ with amplification of *CDK6* (37% of cases) [45].

G4-MBs cells are usually characterized by tetraploid genomes. Among observed chromosomal structural aberrations, the formation of the 17q isochromosome found in approximately 80% of diagnosed cases is detected the most frequently in malignant cells [26]. It should be noted that the presence of the 17q isochromosome does not indicate a poor prognosis for patients [63]. In addition, the chromosomal aberrations detected in G4-MBs are losses in 8p and 10q, gain in chromosome 7, aberrations in 11p and 18q, and even loss of one X chromosome, found in approximately 80% of G4-MBs female patients (Fig. 5D) [48].

CNS Primitive Neuroectodermal Tumours

Atypical Teratoid/Rhabdoid Tumors

Rhabdoid tumors are soft tissue tumors with different localization grouped together because they develop from the mesenchymal cells. Such tumors show rhabdomyoblasts, common histological features of malignant cells. These cells can be of different shapes (from more classical round to polygonal) with large centrally located nuclei and a residual amount of eosinophilic cytoplasm that is often more reminiscent of inclusion [74].

Atypical teratoid/rhabdoid tumors (AT/RTs) are a rare group of pediatric cancers that account for no more than 2% of all cases [75]. Generally, AT/RTs occur in infants, with the peak of incidences from birth up to the age of 2. However, there is a high probability of the AT/RT diagnosis up to the age of 5 [75,76]. AT/RT cases were reported in the adult population; however, it is not possible to speak a percentage of incidences due to low rates and the irregular AT/RT diagnostic in that age group. For example, according to the data from the Massachusetts General Hospital, there were only 54 diagnosed AT/RT cases in people older than 18 between 1987 and 2016 [77]. The gender distribution of AT/RTs is equal, with a slight male preponderance. The clinical prognosis for AT/RT patients is extremely unfavorable; the median survival from the time of diagnosis is about 1 year [78]. It should be noted that such a prognosis strongly depends on the patient's age. The infants' average survival rate of 2 years is up to 5 times lower than that of older children, at about 17% and 89%, respectively [79].

AT/RTs are not associated with any specific location; these tumors can arise in multiple brain sites. AT/RTs were diagnosed within a cerebellopontine angle cistern, meninges, cranial nerves, a spinal canal, extradural location, and infrequently in the pineal gland [80,81]. Thus, it is still unclear what the predominant AT/RT localization site is. There is an opinion on the supratentorial region, while some have proposed the infratentorial region as predominant [82,83]. Histological examination of AT/RT tumor tissue using light microscopy showed similarities with the typical morphology of rhabdoid tumors. However, according to the immunohistochemical analysis and ultrastructural features, cancerous cells show no signs of mesenchymal origin; hence, they are called "atypical" [84].

AT/RTs are extremely malignant embryonal brain tumors with a relatively stable genome compared with other CNS tumors [11]. The most frequent alteration observed in almost all AT/RT cases (approximately 95%) is the bi-allelic loss of function of the *SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1* (*SMARCB1*) gene [85]. However, the remaining 5% of AT/RT cases carry bi-allelic inactivation of *SMARCA4* [86]. These genes encode BAF47 (also known as INI1 and SNF5) and BRG1, respectively, which are structural and functional elements of the SWI2/SNF2 complex of chromatin remodeling. It is well known that SWI2/SNF2 components are frequently mutated in many cancers, and, as we mentioned before, the *SMARCA4* gene is mutated in WNT-MBs [43,44]. It should be emphasized that the presence of the altered BAF47 in the AT/RT group is considered a prognostic marker. Moreover, anti-BAF47 antibodies are used in an immunohistochemical analysis for the outcome prognosis of this disease [11]. Apart from BAF47, the expression of transcription factors FLI-1 and cyclin-D1 was associated with better survival; thus, using these proteins as putative prognostic markers was proposed [87]. The association of cyclin-D1 expression with the AT/RT prognosis was explained with reference to the alterations in the *SMARCB1* gene, which resulted in the promotion of the cell cycle progression caused by downregulation of on expression level of $p16^{INK4a}$, the regulator of G_1/S checkpoint, and concomitant upregulation of *E2Fs* and *Cyclin-D1* which facilitates the G_1/S transition [88].

Moreover, alteration in *SMARCB1* is related to abnormal activation of the SHH and WNT signaling pathways. Wild-type SNF5 could interact with transcription factor GLI1, repressing the latter's functions, leading to the downregulation of the target genes. Thus, there is an upregulation of *GLI1* in a proportion of AT/RTs bearing the mutated *SMARCB*. For this reason, AT/RTs are considered to have a transcription profile similar to that of WNT-MBs [89,90]. As for the WNT signaling pathway, there was hyperactivation of *β-catenin* expression, leading to the loss of the SNF5 functions [90,91].

It was found that SMARCB1 was localized to the nucleus, even though this protein has a nuclear export signal (NES) sequence that should facilitate the SMARCB1 export. However, because of the conformation of the protein structure, its NES becomes masked [92]. In 19% of AT/RT cases, the SMARCB1 protein was localized in the cytoplasm, and there were mutations in a C-terminal domain. Using green fluorescent protein (GFP) fusion, it was demonstrated that mutations in the C-terminal domain caused the unmasking of the NES and translocation of SMARCB1 to the cytoplasm through nuclear pores. Moreover, selective inhibition of exportin-1 resulted in the retention of the mutated SMARCB1 protein within the nucleus [93].

Despite the generally extremely poor prognosis for AT/RT patients, some show a relatively good response to treatment. Molecular heterogeneity within AT/RT cases was hypothesized. Experimental data on DNA methylation profiles and gene expression patterns from almost 200 samples from AT/RT patients allowed us to identify three subgroups: AT/RT-TYR characterized by deletions in *SMARCB1* with no domains of disordered methylation, overexpression of *OTX2* and genes, involved in melanogenesis; AT/RT-SHH characterized by focal aberrations in *SMARCB1* with few domains of disordered methylation and overexpression of *GLI1*; AT/RT-MYC marked by fo-

cal deletions in *SMARCB1* with multiple domains of disordered methylation and overexpression of *MYC* [94,95]. The highest overall survival rates were observed in infants with tumors of the AT/RT-TYR group, while the AT/RT-SHH group was associated with metastases [96]. According to molecular characteristics, nearly all AT/RT cases with the cytoplasmic SMARCB1 belong to the AT/RT-TYR group [93].

Cribriform Neuroepithelial Tumor

A cribriform neuroepithelial tumor (CRINET) represents a rare type of embryonal tumor located predominantly within and around the third or fourth ventricle [97]. This group of embryonal tumors is detected in children with a median age of about 20 months [98]. It is assumed that CRINET arises from the neuroepithelium and is confirmed by the presence of markers such as epithelial membrane antigen, vimentin, microtubule-associated protein 2c (MAP2C), and synaptophysin. However, several important markers of the neuroepithelium, such as neurofilament, neuron-specific enolase, chromogranin A, actin, desmin, TP53, placental alkaline phosphatase, or A-human chorionic gonadotropin were not detected [99].

On the molecular level, CRINET is very similar to AT/RT, especially to AT/RT-TYR; but unlike the latter, their phenotype is non-rhabdoid, meaning that a histological structure of CRINET shows the lack of rhabdoid-like cells, and resembles structures such as cribriform strands and trabeculae [98,99]. The clinical prognosis and the outcome for CRINET patients are relatively favorable, unlike those for AT/RT patients. Thus, the overall survival rate for CRINET patients is 2.5 times higher than that observed for AT/RT patients [98]. The molecular similarity between CRINET and AT/RT is in the deficiency of the *SMARCB1* gene in both groups [100]. So far, little is known about possible additional molecular characteristics for CRINET, and currently, it is difficult to distinguish CRINET and AT/RT in terms of molecular features. These two groups could represent different histological variants but be combined in a single *SMARCB1*-altered group.

Embryonal Tumors with Multilayered Rosettes

Embryonal tumors with multilayered rosettes (ETMRs) represent a highly aggressive group of embryonal brain tumors observed predominantly in infants; 93% of cases are detected in children younger than 3 years. The median survival rate for such patients is 1 year after diagnosis [101]. While ETMRs are a group of tumors with rapid growth and extremely poor prognosis, their incidence rate is generally low, with approximately 1 case per 700,000 children; no statistical data for adults are available [102]. Unlike other embryonal brain tumors predominantly diagnosed in males or equally distributed, the incidence of ETMR is higher in females [46]. Usually, ETMRs are in supratentorial regions (about 70%), while the other 30% are in infratentorial regions [103]. ETMRs are much larger compared with other discussed tumors, clearly demarcated from other brain tissue, may have cystic components, and are usually enriched by extensive intra-tumoral hemorrhage with surrounding edema [104,105].

Tumors of this group are the most histologically heterogeneous and the least studied among all embryonal brain tumors. Examination of ETMRs' histology has indicated separate clusters of small cells with no signs of differentiation; this is similar to ependymoblastic-like rosettes mixed with fibrillar areas, much like neuropil (a nerve fiber weave zone where synapses are formed) [46]. It should be emphasized that prior to the WHO 2016 classification, three different tumor types were distinguished, namely, embryonal tumors with abundant neuropil and true rosettes, ependymoblastoma, and medulloepithelioma, all belonging to primitive neuroectodermal tumors [6]. All listed nosologies carry amplification of the chromosome 19 miRNA cluster (C19MC) at the 19q13.42 locus. It was the reason that they were all grouped as ETMRs [106].

Moreover, in all tested ETMR cases with amplification of *C19MC,* the fusion of *C19MC* with *tweety family member 1* (*TTYH1*) was observed, according to sequencing analysis. *TTYH1* encodes an eponymous protein (a chloride anion channel) required to maintain neural cell stemness. Thus, *TTYH1* has an enhanced promoter in ETMRs cells that are mostly undifferentiated. The *C19MC* gene, located downstream of *TTYH1* and fused with the latter, is also exposed to such an enhanced promoter [107].

As mentioned above, miRNAs located within the C19MC cluster take part in the control of cell stemness, coordinating cell proliferation and survival. These miRNAs are expressed in germline and undifferentiated cells, with the expression gradually decreasing as cell differentiation increases. Thus, their overexpression resulting from the *C19MC* cluster amplification enhances the tumorigenic potential of the cells [108,109]. Besides the *C19MC* amplification, the upregulation of *lin-28 homolog A* (*LIN28A*) is among the key features of ETMRs. The upregulation of *LIN28A* is a hallmark of ETMRs and is used for differential diagnostics in immunohistochemical analysis. It should be noted that *LIN28A* amplification is not unique to ETMRs as it occurs in other brain tumors, for example, AT/RTs and gliomas. However, only in the *C19MC*-altered ETMRs, the expression level of *LIN28A* is very high [106,110,111].

LIN28 is an RNA-binding protein that functions as the inhibitor of the post-transcriptional processing of the Let-7 family of miRNAs [112]. LIN28 consists of an N-terminal cold shock domain (CSD) and a C-terminal CCHC-type zinc knuckle domain (ZKD) encoded by the *LIN28A* and *LIN28B* genes, respectively. Inhibition of Let-7-miRNA occurs through the recognition of NGNNG motif in pre-Let-7-miRNA by two ZKD domains of LIN28 with the further binding of the CSD domain of LIN28 to the closed loop of pre-Let-7-miRNA. As a result, pre-Let-

7-miRNA cannot be processed into an active state [113]. Genes regulated by Let-7-miRNA include oncogenes such as *MYC*, *RAS*, and *high mobility group AT-hook 2* (*HMGA-2*), and factors promoting G_1/S transition, the Cyclin-D1 and Cyclin-D2 [114]. Thus, in summary, overexpression of LIN28A/LIN28B in the C19MC-altered ETMRs leads to the almost total block of Let-7-miRNAs, preventing them from performing their inhibitory functions on oncogene expression, thus maintaining the malignant potential of the transformed cells. In addition, high expression of LIN28 is associated with activating the mammalian target of rapamycin (mTOR) signaling pathways in ETMRs cells, while knockdown of *LIN28* causes a decrease in the expression of several elements of the mTOR pathway [115]. It was reported that in ETMR mouse models with overexpressed LIN28A, the WNT and SHH signaling was enhanced, with concomitant LIN28-dependent downregulation of Let-7-miRNAs [116]. The germline mutations in the *dicer 1, ribonuclease III* (*DICER-1*) gene were also detected in several ETMR cases when no amplification of the *C19MC* cluster was observed [11]. It was demonstrated that the loss of function mutations in *DICER-1* caused R-loop-associated chromosomal instability [117].

Most embryonal tumors diagnosed within CNS belong to one of the groups discussed above— MB, AT/RT, and ETMR. However, certain cases cannot be attributed to any of these groups. These rare types of embryonal tumors are traditionally considered separately and include CNS high-grade neuroepithelial tumors with *meningioma 1* (*MN1*) alteration, CNS high-grade neuroepithelial tumors with *BCL-6 corepressor* (*BCOR*) alteration, and CNS neuroblastoma with *Forkhead box R2 (FOXR2)* activation [118].

CNS Neuroblastoma with FOXR2 Activation (CNS NB-FOXR2)

CNS Neuroblastoma with FOXR2 Activation (CNS NB-FOXR2) is a malignancy with a poor prognosis usually observed among children aged 5–7 years; tumors are localized exclusively in the supratentorial area [11]. Histologically, CNS NB-FOXR2 is a typical neuroectodermal tumor, with round-shaped cells characterized by a large hyperchromatic nucleus and the residual amounts of cytoplasm, forming rosette-like clusters surrounded by branched blood vessels [119].

As the name implies, the key molecular feature of CNS NB-FOXR2 is chromosomal rearrangements that lead to an increase in FOXR2 expression levels [11]. As a result of these rearrangements, the *FOXR2* gene becomes upregulated as it is fused with other genes with enhanced promoters. A set of genes involved in this fusion includes the transcription factors coactivator *jumonji domain containing 1C* (*JMJD1C*), the apoptosis encoding regulator *MAGE family member H1* (*MAGEH1*) gene, the *MAGED2* gene encoding a phosphoprotein and engaged in the alternative splicing, and the *USP51* gene encoding an enzyme involved in the ubiquitination of proteins [118]. It was demonstrated that FOXR2 could bind directly to MYCN, thus promoting and enhancing the MYCN-dependent pro-tumorigenic effect [120]. NB-FOXR2 may be distinguished from other neuroepithelial CNS tumors by the expression of FOXR2, SRY-box transcription factor 10 (SOX10), and the phosphoprotein ankyrin repeat domain 55 (ANKRD55), using the immunohistochemical analysis [121].

CNS High-Grade Neuroepithelial Tumor with MN1 Alteration (CNS HGNET-MN1)

CNS High-Grade Neuroepithelial Tumor with MN1 Alteration (CNS HGNET-MN1) is a recently described rare embryonal tumor located mainly in a supra-tentorial area, affecting predominantly girls (about 90% of cases) [122]. Histologically, CNS HGNET-MN1s are represented as ependymoma-like or astroblastoma-type perivascular pseudo-rosettes, including elongated cells with abundant eosinophilic cytoplasm [119].

The characteristic feature of CNS HGNET-MN1 is a rearrangement of the *MN1* gene in the q arm of chromosome 22. *MN1* encodes the proto-oncogene MN1 (meningioma 1) that was first discovered in meningiomas, where this gene is disrupted due to translocation (4;22) [123]. MN1 functions as the regulator of gene transcriptions through interaction with SMARCA4 (BAF47)—the key element of the SWI/SNF complex for chromatin remodeling. Notably, *SMARCA4* is often altered in other embryonal brain tumors. However, no data on this gene were reported for CNS HGNET-MN1. Thus, *SMARCA4* should be further studied as a putative marker for this group [43,44,86]. Along with the *MN1* rearrangements, the fusion of this gene with the *BEN domain containing 2* (*BEND2*) gene occurs frequently. *BEND2* is located on chromosome Xp22.13 and encodes a DNA-binding protein known as the regulator of mRNA transcription processes [124,125].

CNS High-Grade Neuroepithelial Tumor with BCOR Alteration (CNS-HGNT-BCOR)

CNS High-Grade Neuroepithelial Tumor with BCOR Alteration (CNS-HGNT-BCOR) is an embryonal brain tumor located within the cerebral or cerebellar hemispheres and is often detected in children from 3 to 7 years old [126]. Histologically, CNS-HGNT-BCOR is represented by malignant cells of differently shaped forms, such as spindle or ovoid, characterized by a large nucleus with a scanty cytoplasm [119].

On a molecular level, CNS-HGNT-BCOR cells bear the in-frame internal tandem duplication in exon 15 of the *BCOR* gene or its 3' end, resulting in its upregulation [118]. *BCOR* encodes a protein, functioning as the repressor of BCL-6, a transcription factor, and a proto-oncogene. Interaction between BCOR and BCL-6 occurs as the homomeric binding of two BTB (also known as POZ or ZIN) domains encoded by both proteins. As a result, expression of

	MUTATED GENES	AMPLIFIED GENES	CHROMOSOMAL ABERRATIONS	OTHER GENETIC ABNORMALITIES
WNT-ACTIVATED MEDULLOBLASTOMAS	● β-catenin dependent: *CTNNB1* *APC* *DDX3X* ● β-catenin independent: *SMARCA4*	———	Monosomy 6	———
SHH-ACTIVATED MEDULLOBLASTOMAS	● Germline mutations: *PTCH1* *SUFU* *TP53* ● Somatic mutations: *PTCH1* *SMO* *TERT* *IDH1*	*MYCN* *MYCL1* *GLI2*	● Loss: 9q 10q 17p ● Gain: 3q 9p	———
GROUP 3 OF MEDULLOBLASTOMAS	*SMARCA4* *CTDNEP1* *KBTBD4* *KMT2D*	*MYCN* *MYC* *OTX2*	● Loss: 5q 10q ● Gain: 1q ● Deletion: 10q 11 16q ● Isochromosome: 17q	● Overexpression: *GFI1* *GFI1B*
GROUP 4 OF MEDULLOBLASTOMAS	*KDM6A* *ZMYM3* *KMT2C*	*MYCN* *CDK6*	● Loss: 8p 10q X ● Gain: 7 ● Isochromosome: 17q	● Duplication: *SNCAIP*
ATYPICAL TERATOID/RHABDOID TUMORS	*SMARCB1* *SMARCB4*	———	———	● Overexpression: *GLI1* *MYC* *OTX2*
CRIBRIFORM NEUROEPITHELIAL TUMOR	*SMARCB1*	———	———	———
EMBRYONAL TUMORS WITH MULTILAYERED ROSETTES	*DICER-1*	*C19MC*	———	● Overexpression: *LIN28A*

Fig. 6. A Summarizing scheme of molecular alterations of the common subtypes of embryonal brain tumors. *SMARCB1*, *SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1*; *SMARCB4*, *SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 4*; *DICER-1*, *dicer 1, ribonuclease III*; *LIN28A*, *lin-28 homolog A*.

the BCL-6 target genes, such as *cyclin dependent kinase inhibitor 1A* (*CDKN1A*) and *cyclin dependent kinase inhibitor 1B* (*CDKN1B*), which coordinate the proliferation checkpoints, is downregulated [127,128].

Conclusions

The molecular mechanisms underlying embryonic CNS tumor development are still quite poorly understood. That is why the main task of this paper was to analyze and present an overview of all known information about molecular features of embryonal brain tumors subtypes. Molecular alterations that are characteristic of the various subtypes of embryonal brain tumors are schematically presented in Fig. 6.

It is known that some tumors are caused by alterations in SHH, WNT, and mTOR signaling. Overexpression of the *MYC* and *MYCN* genes is characteristic for many embryonal brain tumors, leading to enhanced cell proliferation and disturbances in the cell cycle. The functioning of the SWI2/SNF2 chromatin remodeling complex are distorted in such malignancies as well. Moreover, *LIN28* is often overexpressed in a set of embryonic CNS tumors. Noteworthy, *LIN28* and *MYC* are involved in the induction of pluripotency. More so-called "Yamanaka" factors, namely, KLF transcription factor 4 (KLF4), organic cation/carnitine transporter4 (OCT4), and SRY-box transcription factor 4 (SOX4) should be analyzed. Besides, a role of the 28S ribosomal protein S18a, mitochondrial (MRPS18) family proteins, and MRPS18-2, which are involved in maintaining cell stemness, in particular, in the development of embryonal brain tumors should be elucidated as well. A study on molecular mechanisms underlying the development of embryonal brain tumors of the CNS will contribute to a creation of personalized therapy.

Author Contributions

VS, LK, EP, TM, and EK collected and analyzed the data; VS has been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors give final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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