

Medulloblastoma

Paul A. Northcott¹, Giles W. Robinson², Christian P. Kratz³, Donald J. Mabbott⁴, Scott L. Pomeroy^{5,6,7}, Steven C. Clifford⁸, Stefan Rutkowski⁹, David W. Ellison¹⁰, David Malkin¹¹, Michael D. Taylor¹², Amar Gajjar² and Stefan M. Pfister^{13,14,15}*

Abstract | Medulloblastoma (MB) comprises a biologically heterogeneous group of embryonal tumours of the cerebellum. Four subgroups of MB have been described (WNT, sonic hedgehog (SHH), Group 3 and Group 4), each of which is associated with different genetic alterations, age at onset and prognosis. These subgroups have broadly been incorporated into the WHO classification of central nervous system tumours but still need to be accounted for to appropriately tailor disease risk to therapy intensity and to target therapy to disease biology. In this Primer, the epidemiology (including MB predisposition), molecular pathogenesis and integrative diagnosis taking histomorphology, molecular genetics and imaging into account are reviewed. In addition, management strategies, which encompass surgical resection of the tumour, cranio-spinal irradiation and chemotherapy, are discussed, together with the possibility of focusing more on disease biology and robust molecularly driven patient stratification in future clinical trials.

Medulloblastoma (MB) is among the most common malignant childhood brain tumours (WHO grade IV). The peak age of diagnosis is ~6–8 years of age, although MB can occur during the first year of life or during adulthood in some individuals. Histomorphologically, MB is an embryonal tumour of the cerebellum, and is suspected to originate from various discrete neuronal stem or progenitor cell populations during early life (FIG. 1).

A multitude of key genetic events have been defined in MB. High-level *MYC* amplifications were among the first recurrent gene-level alterations to be reported, and *MYC* is now considered among the most frequently altered and best characterized oncogenes in MB. Children with *MYC*-amplified MB almost universally fail current therapies. Insights from rare familial tumour syndromes that predispose to MB development (namely, Gorlin syndrome and familial adenomatous polyposis (FAP) syndrome) provided early clues into the genes and pathways involved in MB pathogenesis. For example, germline mutations in *PTCH1* or *SUFU* (which are negative regulators of the sonic hedgehog (SHH) signalling pathway) predispose to Gorlin syndrome, and both genes are recurrently mutated in MB in the germ line and somatically, substantiating a causative role for SHH signalling in some patients with MB. In addition, defective WNT signalling has been implicated in MB pathogenesis owing to the presence of *APC* germline mutations (which predispose to FAP) in ~1% of patients and somatic mutations in *CTNNB1* in ~7% of patients.

Early gene expression array studies confirmed that MB was molecularly distinct from other embryonal brain tumours such as atypical teratoid rhabdoid tumour (AT/RT) and supratentorial primitive neuroectodermal tumour (PNET)¹. Subsequent expression profiling identified discrete molecular subgroups within MB^{2–6}, and in 2012 a consensus⁷ on MB subgroups emerged proposing the following four subgroup designations: WNT-MB, SHH-MB, Group 3 MB and Group 4 MB (BOX 1). These consensus subgroup definitions have since been adopted by both the basic and clinical research communities, changing the way MB is studied in the laboratory and augmenting the way in which the disease is diagnosed and managed in the clinic. In 2016, the WHO incorporated consensus MB subgroups into the updated edition of the *Classification of Tumors of the Central Nervous System*⁸. More recent data have revealed the presence of SHH, Group 3 and Group 4 MBs subtypes on the basis of molecular heterogeneity, differences in age at MB onset and prognosis.

MB diagnosis is based on clinical symptoms, imaging, cerebrospinal fluid (CSF) cytology and an integrated histopathology and molecular analysis. Standard-of-care therapy for MB includes surgical resection to remove the tumour, cytotoxic chemotherapy and, in non-infants (usually defined as patients ≥3 years of age), cranio-spinal irradiation (CSI). Treatment outcome is strongly associated with patient age and a series of established and evolving clinicopathological and molecular features. Five-year overall survival for standard-risk patients, typically defined as patients >3 years of age who have a gross total

*e-mail: s.pfister@kitz-heidelberg.de
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Author addresses

- ¹Department of Developmental Neurobiology, Neurobiology and Brain Tumor Program, St. Jude Children's Research Hospital, Memphis, TN, USA.
- ²Department of Oncology, Neurobiology and Brain Tumor Program, St. Jude Children's Research Hospital, Memphis, TN, USA.
- ³Department of Paediatric Haematology and Oncology, Hannover Medical School, Hannover, Germany.
- ⁴Neurosciences and Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada.
- ⁵Department of Neurology, Boston Children's Hospital, Boston, MA, USA.
- ⁶Department of Neurology, Harvard Medical School, Boston, MA, USA.
- ⁷Eli and Edythe Broad Institute of MIT and Harvard, Cambridge, MA, USA.
- ⁸Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK.
- ⁹Department of Paediatric Haematology and Oncology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany.
- ¹⁰Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA.
- ¹¹Division of Haematology/Oncology, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.
- ¹²Developmental and Stem Cell Biology Program, The Arthur and Sonia Labatt Brain Tumour Research Centre, Division of Neurosurgery, Departments of Surgery, Laboratory Medicine and Pathobiology, and of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada.
- ¹³Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany.
- ¹⁴Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany.
- ¹⁵Department of Hematology and Oncology, Heidelberg University Hospital, Heidelberg, Germany.

resection (GTR) of their tumour and are non-metastatic at diagnosis, is 70–85%^{9–11}. Patients who are <3 years of age, have a subtotal resection (STR) of their tumour and/or are metastatic at diagnosis are considered to be of high risk and often have 5-year overall survival <70%^{9,12,13}. Owing to the severe neurocognitive, neuroendocrine and psychosocial deficits that can be attributed to current standard-of-care treatment for MB, there is intensive motivation on the part of clinicians treating MB and scientists studying the biology of MB to identify improved therapeutic strategies that are less toxic and more effective at curing patients of their disease.

This Primer discusses the epidemiology, molecular pathogenesis, diagnosis and management of MB, taking the four consensus subgroups into account, and describes the more recent discovery of MB subtypes, as well as the need to incorporate these subtypes into routine clinical practice.

Epidemiology

MB comprises ~63% of childhood intracranial embryonal tumours and has an annual incidence of ~5 cases per 1 million individuals¹⁴. The age-specific incidence peaks in the age groups of 1–4 years and 5–9 years, with a median age at diagnosis of ~6 years of age¹⁵. Rarely, MB is diagnosed in adults with an incidence of 0.05 cases per 100,000 individuals¹⁶. Overall, MB is more common in males than in females, with a 1.8:1 male:female ratio, although the sex predominance differs between MB subgroups^{15,17,18} (BOX 1). Approximately 18% of patients develop subsequent neoplasms within 30 years of MB diagnosis, which might partly be explained by hereditary predisposition¹⁹. Although population-based studies are scant, there do not appear to be any substantial differences in MB incidence across ethnicities or geographical regions^{20,21}.

Risk factors

Environmental causes of MB remain largely unknown, and heritable factors represent the only proven risk factors. A wide spectrum of Mendelian conditions increase the risk of MB due to germline mutations in genes involved in developmental signalling pathways and molecular processes that are implicated in MB pathogenesis (FIG. 2). These conditions include syndromes with a role in SHH signalling, such as Gorlin syndrome^{22–24}, Curry-Jones syndrome²⁵ and Greig cephalopolysyndactyly syndrome^{26,27}; WNT signalling, such as FAP syndrome²⁸; DNA damage response and repair, such as ataxia telangiectasia²⁹, Bloom syndrome³⁰, constitutional mismatch repair deficiency³¹, Fanconi anemia³², Li-Fraumeni syndrome³³, Nijmegen breakage syndrome³⁴ and xeroderma pigmentosum³⁵; and chromatin remodelling and/or transcription factor recognition, such as Rubinstein-Taybi syndrome³⁶.

Pathogenetic germline variants of *APC*, *BRCA2*, *PALB2*, *PTCH1*, *SUFU* and *TP53* were found in 5.9% of MBs in one study of 1,022 patients, many of whom had no clinically recognized cancer predisposition syndrome¹⁹. Owing to the rarity of the underlying genetic conditions and the lack of natural history studies, the precise MB risk associated with germline mutations in these genes is poorly understood. However, the risk of MB, which is predicted to depend on the precise mutation type and the presence of genetic, epigenetic and environmental risk factors, is highest in carriers of mutations in *SUFU* and *TP53* and biallelic mutations in *BRCA2* and *PALB2* (REF. ¹⁹). In carriers of *APC* or *PTCH1* mutations, or those with heterozygous mutations in *BRCA2* or *PALB2*, the risk of MB is only moderately increased¹⁹. In patients with MB and suspected germline predisposition, the age at diagnosis, molecular subgroup and somatic MB signatures largely depended on the type of the inherited defect¹⁹. Damaging mutations in *SUFU* or, more rarely, *PTCH1* (diagnostic of Gorlin

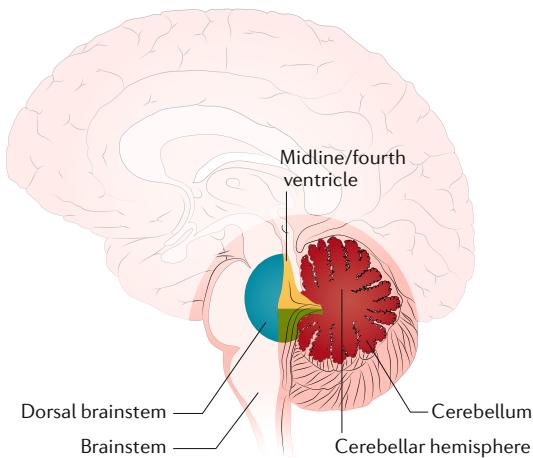


Fig. 1 | Location of MB. Sagittal section of the cerebellum and brainstem, with common diagnostic locations of medulloblastoma (MB) indicated on the basis of MRI. MB locations have been colour-coded according to prominent diagnostic locations observed for individual consensus subgroups: WNT (blue); SHH (red); Group 3 (yellow); Group 4 (green).

Box 1 | The consensus subgroups of MB

WNT subgroup

WNT-medulloblastoma (MB) accounts for ~10% of all MB diagnoses, manifests after 4 years of age, including in adulthood, and has a fairly balanced male:female ratio⁷.

WNT-MB tumours are infrequently metastatic at diagnosis, and the prognosis for patients <16 years of age is excellent as >95% survive beyond 5 years^{4,9,43,209,210}. By contrast, adults with WNT-MB can have a less favourable outcome^{5,211}.

SHH subgroup

Sonic hedgehog (SHH)-MB is the dominant molecular subgroup in infants (<3 years of age) and adults (>16 years of age) and accounts for approximately two-thirds of cases in these age groups¹⁰⁴. SHH-MB is less common during childhood and adolescence, representing only ~10–15% of MB diagnoses during these periods. The male:female ratio for SHH-MB is slightly biased towards males⁷. Large-scale DNA methylation profiling studies have demonstrated that infant and childhood SHH-MBs represent clinically and biologically distinct groups, with an empirical age cut-off of 3–5 years of age between the two⁶². Prognosis for SHH-MB is strongly dependent on patient age, tumour histology, metastatic status and genotype.

Group 3 subgroup

Group 3 MB accounts for ~25% of all patients with MB and is especially common during infancy and early childhood. Group 3 MB is twice as common in males as in females⁷. A high incidence of metastasis at diagnosis is characteristic of Group 3 MB and is a strong predictor of inferior outcome. Group 3 MB is considered the most aggressive subgroup of MB, with 5-year overall survival of <60%^{2,6}; the presence or absence of different molecular, genetic and clinical features strongly correlates with outcome.

Group 4 subgroup

Group 4 MB is the most common subgroup of MB, accounting for ~35–40% of patients and almost 50% of adolescent patients. Group 4 MB is more common in males than females, with a male:female preponderance of ~3:1 (REF.⁷). Approximately one-third of patients with Group 4 MB are metastatic at diagnosis, and patients who relapse tend to relapse >5 years after their original diagnosis. Survival for Group 4 MB is generally considered intermediate, although several different risk groups have been proposed on the basis of cytogenetics, molecular subtype or a combination of the two (see Mechanisms/pathophysiology).

syndrome) were found in 21% of patients <3 years of age with SHH-MB, whereas germline *TP53* mutations (diagnostic of Li-Fraumeni syndrome and restricted to patients with SHH-MB) were found in 24% of patients 5–14 years of age with SHH-MB, and mutations in *APC* (diagnostic of FAP syndrome) were found in 7.4% of patients with WNT-MB¹⁹ (FIG. 2).

Mechanisms/pathophysiology

Genetic–epigenetic interplay

Although detailed functional studies remain in their infancy, alterations in chromatin-modifying genes appear to be a common and converging mechanism underlying MB pathogenesis. A series of rare focal copy-number alterations affecting histone-modifying genes, such as *EHMT1*, *SMYD4*, *L3MBTL3*, *KDM4C* (also known as *JMJD2C*) and *KAT6A* (also known as *MYST3*)³⁷, were reported initially (FIG. 3). Similarly, recurrent mutations in *KMT2D* (also known as *MLL2*), *KMT2C* (also known as *MLL3*), *SMARCA4* and other genes were identified in MB tumours by gene re-sequencing³⁸. Moreover, germline mutations that predispose to MB development, such as those in *CREBBP* and *EP300*, are involved in histone modifications. Mutations and structural variants targeting a range of different chromatin-modifying genes have been discovered, and it is estimated that nearly half of all MBs harbour a clonal somatic alteration in at least one chromatin

regulator^{39–41}. Many of these genes and the complexes in which they are suspected to function are altered in a subgroup-specific manner.

MB subgroups

WNT subgroup. Approximately 85–90% of WNT-MBs harbour somatic activating mutations in exon 3 of *CTNNB1* (encoding β-catenin), leading to constitutively active WNT signalling through stabilization of β-catenin (FIG. 4). Stabilized β-catenin accumulates in the nucleus, where it acts as a co-activator for transcription factors of the TCF–LEF family, leading to upregulation of WNT-responsive genes that drive cell growth and proliferation^{4,42}. To date, all of the engineered mouse models of WNT-MB rely on *Ctnnb1* and *Tp53* mutations, supporting the essential role of these genes in WNT-MB development (BOX 2). Patients with WNT-MB who lack somatic *CTNNB1* mutations often harbour pathogenetic constitutional variants of the tumour suppressor gene *APC*¹⁹. APC functions in a complex containing axin 1, axin 2, CSNK1A1 and GSK3β that promotes phosphorylation-dependent ubiquitylation and degradation of β-catenin, which explains the constitutively activated WNT signalling observed in patients with MB and *APC* loss-of-function mutations¹⁹. Another hallmark feature of WNT-MB is monosomy 6, which is found in ~80–85% of patients and usually co-occurs with *CTNNB1* mutations^{4,42–44}. Aside from monosomy 6, WNT-MB genomes are usually balanced and focal gene-level amplifications and deletions are exceedingly rare⁴⁴.

Patients with WNT-MB have the second highest burden of somatic genome-wide single-nucleotide variants (SNVs) out of all MB subgroups, with an average of ~1,800 per genome⁴⁵. Several recurrently mutated genes have been identified, most notably, *DDX3X* (in 36% of patients), *SMARCA4* (also known as *BRG1*; 19%), and *TP53* (14%), as well as clinically actionable mutations in *CSNK2B* (14%), *PIK3CA* (encoding the catalytic subunit of phosphatidylinositol 3-kinase; 11%) and *EPHA7* (8%)^{42,45–47} (FIG. 4). *DDX3X* encodes a DEAD-box RNA helicase, which is also commonly mutated in patients with SHH-MB. Somatic *DDX3X* mutations found in WNT-MB tumours might contribute to tumorigenesis by increasing the proliferation of lower rhombic lip progenitor cells⁴⁷, which are considered the putative cells of origin for WNT-MB⁴⁸, and through the deregulation of translation⁴⁹. *SMARCA4* encodes a central subunit of SWI–SNF chromatin remodelling complexes that modulate transcription by altering local chromatin structure. SWI–SNF complex genes are estimated to be mutated in ~20% of all human cancers⁵⁰. The prevalent *SMARCA4* mutations in WNT-MB, along with mutations in related SWI–SNF complex subunits (such as *ARID1A* and *ARID2*), suggest that deregulation of SWI–SNF-mediated chromatin remodelling is an important cooperating event in WNT-driven MB. In terms of potential clinically actionable mutations, *CSNK2B* encodes the β-subunit of casein kinase II (CKII), which regulates a range of cellular processes, including metabolism, signalling, transcription, translation and replication^{51,52}. CKII positively regulates WNT signalling through

multisite phosphorylation of dishevelled, β -catenin and the TCF–LEF family of transcription factors^{51,52}. Similar to SMARCA4, somatic mutations in PIK3CA are found in a wide variety of human cancers⁵³, and this gene functions as an oncogene owing to constitutive activation of downstream AKT and mTOR signalling, resulting in aberrant cellular growth, proliferation, survival, motility and more⁵⁴. *EPHA7* encodes a member of the ephrin receptor subfamily of protein-tyrosine kinases, which are highly expressed in the developing central nervous system (CNS) and contribute to spatial organization of neuronal populations, tissue patterning, axon guidance and synaptogenesis⁵⁵; the functional implications of these mutations in MB development are currently unknown.

Many patients with WNT-MB have an excellent prognosis, which may be partly due to alterations in the brain vasculature in these patients. Indeed, in a series of elegant studies of human and mouse WNT-MBs, WNT-MBs lacked an intact blood–brain barrier (BBB) and were characterized by aberrant vasculature networks caused by overproduction of WNT antagonists (such as *WIF1* and *DKK1*) that block WNT signalling and BBB specification in surrounding endothelial cells⁵⁶. The ‘leaky’ fenestrated vasculature that is characteristic of WNT-MBs provides a plausible explanation for the often-haemorrhagic phenotype of these tumours at the time of their surgical resection and was suggested to render them more accessible to systemic chemotherapies, although this requires further validation.

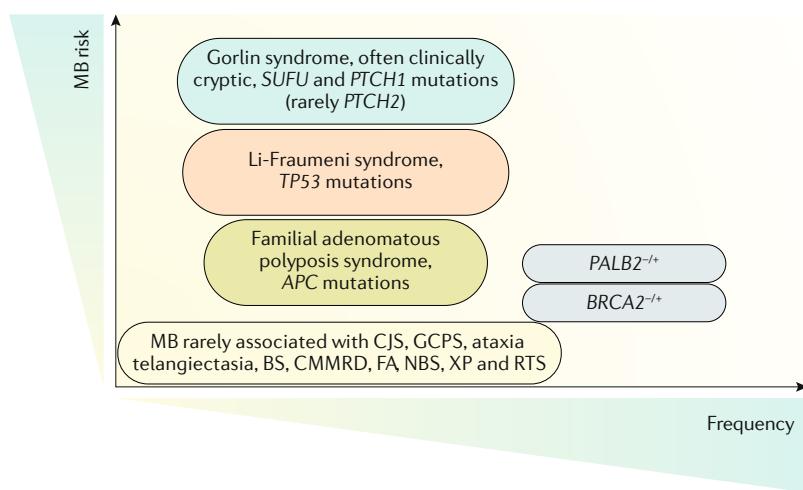


Fig. 2 | MB predisposition. To date, germline mutations in six genes have been associated with a significantly increased risk of medulloblastoma (MB): *TP53* (associated with Li-Fraumeni syndrome), *PTCH1* and *SUFU* (associated with Gorlin syndrome), *APC* (associated with familial adenomatous polyposis syndrome) and *PALB2* and *BRCA2* (associated with subsets of Fanconi anaemia). Other syndromes are associated with increased risk of MB in rare cases, such as Curry–Jones syndrome (CJS; caused by mosaic *SMO* mutations), Greig cephalopolysyndactyly syndrome (GCPs; caused by mutations in *GLI3*), ataxia telangiectasia (caused by *ATM* mutations)²⁹, Bloom syndrome (BS; caused by *BLM* mutations)³⁰, constitutional mismatch repair deficiency (CMMRD; caused by mutations in *MSH2*, *MSH6*, *MLH1* and *PMS2*)³¹, Fanconi anaemia (FA; caused by mutations in *FANCA-W*), Nijmegen breakage syndrome (NBS; caused by mutations in *NBN*), xeroderma pigmentosum (XP; caused by mutations in *DDB2*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *POLH*, *XPA* and *XPC*) and Rubinstein–Taybi syndrome (RTS; caused by mutations in *CREBBP* and *EP300*). Most published studies have focused on high-penetrance alleles, which are exceedingly rare in the general population, whereas large genome-wide association studies for MB are lacking to date.

SHH subgroup. Genetically, the SHH-MB subgroup is among the best understood, with the majority of patients harbouring either germline or somatic mutations and copy-number alterations in critical genes of the SHH signalling pathway (FIG. 5). These mutations include loss-of-function mutations or deletions in *PTCH1* (43% of patients), loss-of-function mutations or deletions in *SUFU* (10%), activating mutations in *SMO* (9%), *GLI1* or *GLI2* amplifications (9%) and *MYCN* amplifications (7%)^{33,42}. Alterations of these and related genes lead to the constitutive, ligand-independent activation of SHH signalling, mitigating the downstream upregulation of SHH-responsive genes that drive cell growth and proliferation. In addition, alterations in many of these genes lead to the formation of SHH-MBs in mice (BOX 2). Recurrent focal copy-number alterations affecting components of the p53 and receptor tyrosine kinase–PI3K pathways have also been reported in SHH-MB. In general, deregulation of p53 signalling is known to promote defects in cell-cycle regulation, apoptosis and DNA repair, whereas aberrant PI3K signalling promotes cellular growth, proliferation, survival and more⁴⁴.

Hallmark cytogenetic events in SHH-MB include losses of the long arms of chromosome 9 (9q) and 10 (10q), which lead to the loss of heterozygosity of critical tumour suppressor genes such as *PTCH1* (located at 9q22) and *SUFU* (located at 10q24), respectively, both of which encode negative regulators of SHH signalling, and potentially others⁵⁷. *TERT* promoter mutations (which affect telomere maintenance) are found in ~39% of patients with SHH-MB and are more prevalent in this subgroup than any other subgroup (<5% of non-SHH patients)^{42,58,59}. Notably, 98% of adult SHH-MBs harboured somatic *TERT* promoter mutations, whereas these mutations were found in 13% of SHH-MBs in infants and 21% in children³³. The implications of this age-associated bias of *TERT* promoter mutations in SHH-MB are currently unknown but suggest that alternative mechanisms of telomere maintenance are active in infants and children with SHH-MB.

Unlike WNT-MB, which is generally considered to be molecularly homogeneous, SHH-MB exhibits biologically and clinically relevant heterogeneity in the form of molecular subtypes^{33,60,61}. These subtypes have varying cytogenetics, demographics and overall survival. Recently, four independent subtypes of SHH were described (SHH α , SHH β , SHH γ and SHH δ) using DNA methylation and gene expression array data sets⁶⁰. In addition, infant and childhood SHH-MBs represent distinct disease groups⁶². In young children (≤ 5 years of age) with MB, two distinct subtypes of infant SHH (iSHH), called iSHH-I and iSHH-II, have been identified. iSHH-I tumours occur more commonly in the youngest infants and are enriched for germline or somatic *SUFU* mutations and chromosome 2 gain, whereas iSHH-II tumours are enriched for activating *SMO* mutations and mutations in chromatin-modifying genes such as *KMT2D* and *BCOR*⁶³ (FIG. 3). These results are in agreement with the molecular features of SHH β and SHH γ ⁶⁰, respectively, suggesting that iSHH-I equates to SHH β and iSHH-II equates to SHH γ . Importantly, the prognosis of these subgroups differed in one clinical

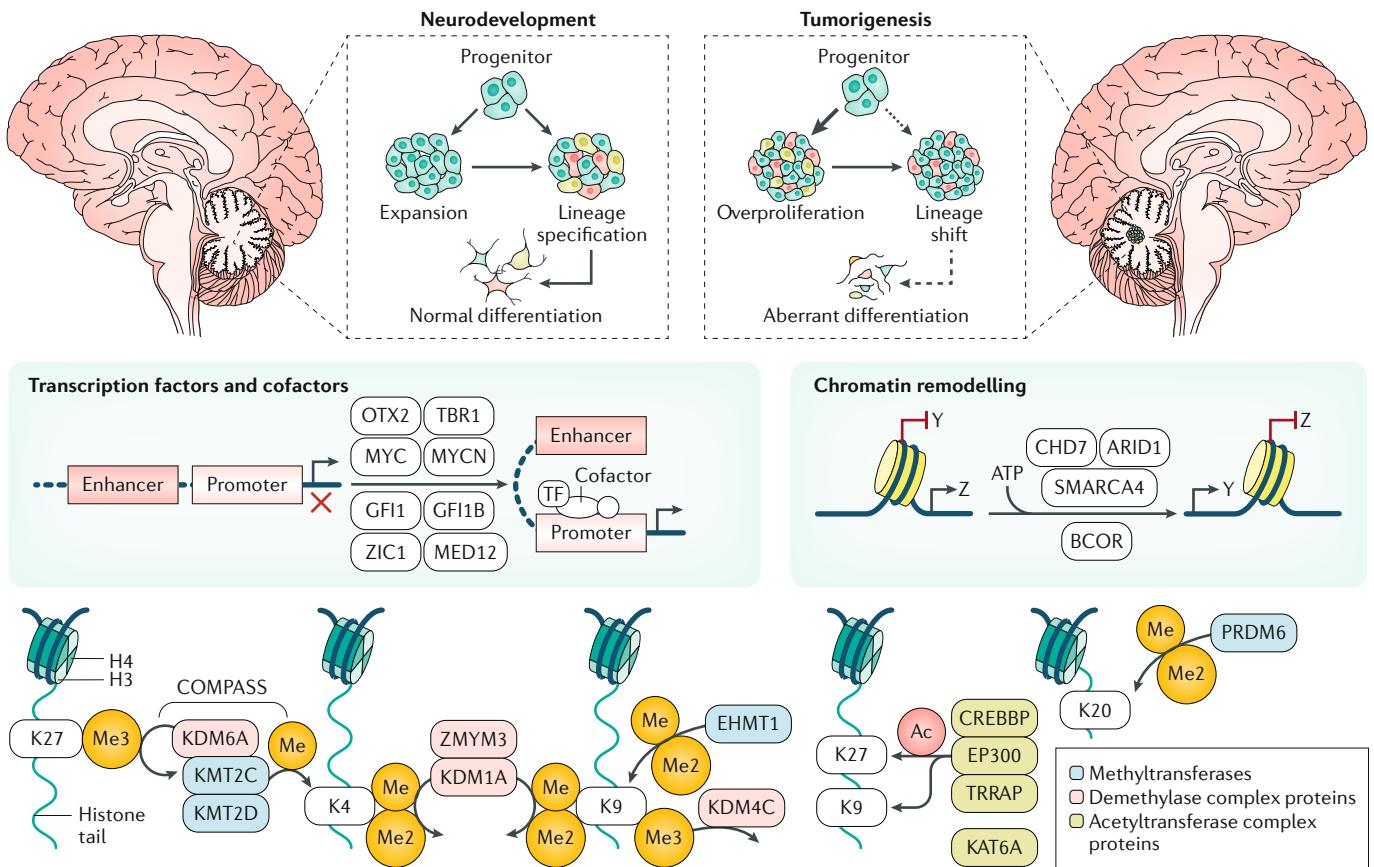


Fig. 3 | Histone-modifying genes and epigenetic alterations in MB. Normal neurodevelopment occurs as the interplay among various spatiotemporally concerted processes that are fundamentally dysregulated in medulloblastoma (MB) tumorigenesis (top panel; dashed lines). These processes are regulated by the cooperative effects of transcription factors and proteins involved in chromatin remodelling (central panel) and histone modification (bottom panel), all of which are genetically altered in MB. The failure to coordinate transcriptional outputs, chromatin accessibility and chromatin structure underlies the key pathophysiological derangements seen in MB, implicating mutations in genes involved in shaping chromatin architecture as key drivers of tumorigenesis. Ac, acetyl group; Me, methyl group; TF, transcription factor.

trial for young children with newly diagnosed MB (SJYC07; NCT00602667); patients with iSHH-II exhibited a 5-year progression-free survival (PFS) of 75.4%, whereas those with iSHH-I had a 5-year PFS of 27.8%⁶³. Validation of these findings in further and expanded cohorts is a key goal.

Older children and adolescents with SHH-MB harbour a preponderance of germline and somatic *TP53* mutations (and rare focal deletions) that are rarely found in infants and adults with SHH-MB^{33,42,62}. These *TP53* loss-of-function mutations and deletions are often coincident with *MYCN* and/or *GLI2* amplification, large cell/anaplastic (LC/A) histopathology (see Diagnosis, screening and prevention) and ‘catastrophic’ chromosomal rearrangements known as chromothripsis⁶⁴. In contrast to patients with WNT-MB harbouring *TP53* mutations who have an excellent prognosis^{65,66}, those with SHH-MB and germline or somatic *TP53* mutations have poor survival, with few exceptions⁶⁷. Reasons underlying these differences in outcome regarding *TP53* mutation status remain poorly understood but might be attributable to divergent developmental origins⁴⁸ for WNT-MB and SHH-MB and potentially

distinct consequences of *TP53* mutations in different cell types. As a result, patients with SHH-MB and *TP53* mutations have garnered their own category by the WHO and are currently considered a very-high-risk group⁶⁸ (BOX 3).

Adults with SHH-MB tend to have a higher burden of genome-wide SNVs than younger patients with SHH-MB, and >80% of adult patients harbour alterations in either *PTCH1* or *SMO*³³. Given that these mutations occur upstream in the SHH pathway, adults with SHH-MB are excellent candidates for molecularly targeted therapy with SMO inhibitors, which have shown encouraging results in clinical trials^{69–73}. However, SHH signalling has an essential role during development, and younger patients treated with SMO inhibitors have severe growth plate complications, halting the use of these agents in skeletally immature patients⁷⁴.

Group 3 subgroup. High-level *MYC* amplification is a defining feature of Group 3 MBs and occurs in ~17% of patients (FIG. 6) but is exceedingly rare in other MB subgroups^{42,44}. Multiple transcriptional and proteomic signatures are associated with *MYC* activation in patients

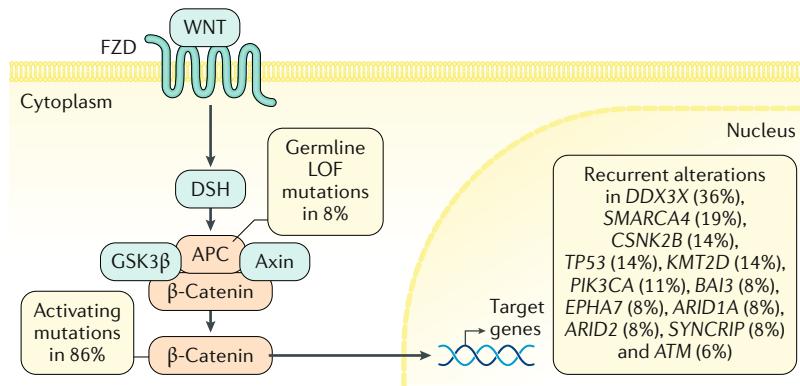


Fig. 4 | WNT subgroup. Several genes of the canonical WNT signalling pathway are altered in the WNT subgroup of medulloblastoma (MB)⁴². APC, promotes degradation of β-catenin; axin, constituent of β-catenin destruction complex; β-catenin, essential mediator of canonical WNT signalling pathway; DSH (dishevelled), cytoplasmic phosphoprotein that transduces WNT signal; FZD (frizzled), receptor for WNT ligand; GSK3β, constitutively active protein kinase that targets β-catenin for degradation; LOF, loss-of-function. The percentage values denote the proportion of patients with WNT-MB who have the associated genetic mutation.

with Group 3 MB, including increased abundance of ribosomal proteins and ribosome assembly proteins, mitochondrial ribosomal proteins and proteins involved in mRNA processing, transcription and translation^{75,76}.

Gene-level somatic mutations are less common in Group 3 MB, with *SMARCA4* (in 9% of patients), *KBTBD4* (6%), *CTDNEP1* (5%) and *KMT2D* (5%) representing the only genes mutated in >5% of patients with Group 3 MB⁴². *KBTBD4* is a poorly characterized Kelch-BTB-BACK family protein that might function as part of the ubiquitin-proteasome system. Somatic mutations in *KBTBD4* usually occur as in-frame insertions clustered in the Kelch domain, potentially affecting its ability to interact with other proteins and/or substrates⁴², although further biochemical and functional studies are required to better understand both the normal and tumorigenic properties of *KBTBD4*. *CTDNEP1* (also known as dullard) is a member of a family of protein phosphatases that dephosphorylate target substrates, including BMP receptors⁷⁷, and might be a positive regulator of WNT signalling for the formation of primordial germ cells in mice⁷⁸. Functional studies of *CTDNEP1* in MB are lacking but are required to gain insight into the role of these mutated proteins in the pathogenesis of Group 3 MB.

Other notable driver events in Group 3 MB include amplifications of *MYCN* (5% of patients) and *OTX2* (3%). The *OTX2* transcription factor has an essential role in the development of the forebrain, hindbrain, eye and pineal gland^{79,80}. *OTX2* functions as a master transcriptional regulator, or pioneer factor, that is highly overexpressed in Group 3 MBs and Group 4 MBs (irrespective of genomic amplification) and that is presumed to maintain MB cells in a stem and/or progenitor-like state, repressing neuronal differentiation and promoting cell-cycle programmes through gene regulation^{81–85}. Structural variants associated with ‘enhancer hijacking’ (whereby structural variants result in the proximity of normally distant coding genomic regions and enhancers

or super-enhancers, leading to gene overexpression) lead to profound, mutually exclusive upregulation of *GFI1* and *GFI1B* in ~15–20% of Group 3 MBs⁸⁶. *GFI1* and *GFI1B* are transcriptional repressors that regulate cell fate decisions in the haematopoietic system. Viral-mediated overexpression of either *GFI1* or *GFI1B* in combination with *MYC* overexpression in mouse neural stem cells promoted the formation of aggressive Group 3-like MBs with complete penetrance and short latencies when implanted into the hindbrains of immunocompromised mice⁸⁶ (BOX 2). Cytogenetically, Group 3 MBs exhibit extensive aneuploidy, characterized by frequent isochromosome 17q (~40–50%; whereby the q arm is duplicated and the p arm is lost); gain of chromosomes 1q and 7; and loss of chromosomes 8, 10q and 16q (REF.⁴⁴).

Multiple different subtypes of Group 3 MB have been proposed^{2,42,60,62}. The first study divided patients with Group 3 MB into two subclasses, designated c1 and c5, on the basis of discriminatory gene expression profiles². c1 was strongly associated with *MYC* amplification or overexpression and was characterized by a poor outcome, whereas c5 had genome-wide aneuploidy and a more favourable outcome. In other studies, two subtypes of Group 3 MB (designated MB_{Grp3-HighRisk} and MB_{Grp3-LowRisk} (REF.⁶²)) or three subtypes (designated Group 3α, Group 3β and Group 3γ⁶⁰) have been reported. In both of these studies, subtypes with *MYC* amplification or overexpression were associated with poor outcomes, and additional subtypes with intermediate to favourable subtypes were identified.

Group 4 subgroup. Similar to what has been reported for Group 3 MB, somatic gene-level mutations are rare in Group 4, with no single gene found to be mutated in >10% of cases⁴². The most prevalent putative driver event involves enhancer-hijacking-mediated overexpression of *PRDM6*, which is found in ~17% of patients⁴² (FIG. 7). In affected Group 4 MBs, *PRDM6* overexpression is tightly associated with focal tandem duplication of *SNCAP* located ~500 kb upstream of the *PRDM6* promoter, suggesting that such structural variation underlies the observed gene activation^{42,44}. *PRDM6* is a chromatin-modifying protein that functions as a transcriptional repressor in vascular and smooth muscle progenitors^{87,88}, although the precise contribution of aberrant *PRDM6* expression to Group 4 MB pathogenesis has yet to be functionally substantiated. Other notable somatic mutations in Group 4 MB, many of which involve histone-modifying genes (FIG. 3), include mutations in *KDM6A* (also known as *UTX*; 9% of Group 4 patients), *ZMYM3* (6%), *KMT2C* (6%) and *KBTBD4* (6%), as well as amplifications of *MYCN* (6%), *OTX2* (6%), *CDK6* (6%) and enhancer-hijacking-associated *GFI1* and/or *GFI1B* overexpression (~5–10%)⁴².

KDM6A, *ZMYM3* and *KMT2C* loss-of-function mutations and rare deletions are mostly mutually exclusive in Group 4 MB and rarely occur in patients with non-Group-4-MB^{41,42}. Interestingly, all three genes encode chromatin-modifying proteins, suggesting that their apparent convergent deregulation is an important mechanism underlying Group 4 MB pathogenesis,

although further studies are required to confirm this hypothesis. CDK6 is a cell-cycle regulator that, along with CDK4, drives G1–S transition^{89,90}. Treatment of MB models with CDK4/CDK6 inhibitors has shown encouraging results in preclinical studies^{91–93} and is now being tested in clinical trials of patients with relapsed MB (NCT03434262). Large-scale chromosomal aberrations are common in Group 4 MB, especially gains of chromosome 7 (40–50% of patients) and 17q (>80%) and deletions of chromosomes 8 (40–50%), 11 (>30%) and 17p (>75%)⁴⁴. Similar to Group 3 MB, isochromosome 17q is found in most Group 4 MBs, the biological

Box 2 | Models of MB

WNT-MB

Mouse models of WNT-medulloblastoma (MB) rely on targeted expression of mutant *Ctnnb1* combined with at least one additional genetic perturbation in lower rhombic lip progenitor cells of the developing mouse hindbrain. Indeed, transgenic mice expressing a constitutively active *Ctnnb1* and lacking *p53* develop low-penetrant, classic MBs that are confined to the dorsal brainstem⁴⁸. Addition of a constitutively active *Pik3ca* allele to these models increased the incidence of murine WNT-MBs from <15% to 100% and reduced the average latency to tumour onset from ~11–12 months to <3 months⁴⁷. To date, all published WNT-MB genetically engineered mouse models include the concomitant mutation of *Ctnnb1* and *Tp53*, and models that include alterations in genes that cooperate with constitutively active WNT signalling in patients (such as *Ddx3x* and *Smarca4*, among others) are lacking.

SHH-MB

Several transgenic mouse models of sonic hedgehog (SHH)-MB have been described^{212–214}. Germline deletions of *Ptch1* lead to MB development in ~15–20% of mice by 6 months²¹⁵, and when combined with *Trp53* deletions lead to MB in ~100% with a latency of <3 months²¹⁶. Several other models are driven by constitutively active *Smo*^{217–219}, *Mycn* overexpression²²⁰ and *Sufu* deletion²²¹, among others. Extensive molecular and cellular characterization of these and related models has confirmed cerebellar granule neuron progenitors (CGNPs) as the probable cell of origin for SHH-MB^{222,223}. For example, *Ptch1*^{+/−} mice have a persistent external granular layer (EGL) in the cerebellum (which undergoes expansion and proliferation of CGNPs) and develop preneoplastic lesions in the EGL, which transform into MBs in ~20% of mice^{224,225}. A rare quiescent population of SOX2-positive cells has been identified in SHH-MBs that are resistant to treatment and potentially responsible for driving tumour regrowth and relapse, suggestive of a cancer stem cell hierarchy within these tumours²²⁶.

Group 3

Targeted *Myc* overexpression in combination with *Trp53* loss-of-function in various neuronal stem and/or progenitor cell populations results in mouse MBs that resemble MYC-driven Group 3 MB (REFS^{227–229}). Models with *Gfi1* or *Gfi1b* expression also produce highly penetrant MBs that recapitulate molecular and phenotypic features of Group 3 MB⁸⁶. In addition, a tetracycline-regulatable *Mycn* overexpression transgenic model²²⁰ that produces both SHH and, more commonly, spontaneous non-WNT/non-SHH-MBs that are molecularly similar to Group 3 MB has been described²³⁰. To date, all mouse models of Group 3 MB depend on the high-level expression of either *Myc* or *Mycn*, which do not adequately recapitulate the molecular and clinical heterogeneity of this subgroup⁴², warranting the pursuit of additional, distinct models. The cellular origins of Group 3 MB and its associated subtypes have yet to be definitively confirmed and might prove prerequisite for the generation of additional, non-*Myc*/*Mycn*-driven models.

Group 4

No accepted transgenic models of Group 4 MB are available, and the cellular origins of this subgroup have yet to be definitively proved. By annotating the active regulatory landscape of MB subgroups, master transcription factors that are largely specific to Group 4 (namely, LMX1A, EOMES and LHX2) have been identified²³¹. These transcription factors have critical roles during neuronal development and, on the basis of their lineage-specific and spatiotemporal expression patterns in the developing cerebellum, have implicated glutamatergic upper rhombic lip progenitors or their derivatives as putative cells of origin for Group 4 MB. As Group 4 MB is the largest MB subgroup, accurate models recapitulating the genetic and epigenetic heterogeneity seen in this subgroup are an area of intensive study within the MB community.

importance of which remains to be defined. Aberrant ERBB4–SRC signalling has been proposed as a new hallmark of Group 4 MB⁷⁶, although functional validation of this feature as a potential therapeutic vulnerability is still ongoing.

As with Group 3 MB, several subtypes of Group 4 MB have been reported^{42,60,62}. Two subtypes (Group 4_{High-risk} and Group 4_{Low-risk}) were reported in one study⁶², whereas another identified three subtypes (Group 4α, Group 4β and Group 4γ)⁶⁰. These subtypes have variable cytogenetics and patient demographics, and the high-risk and low-risk subgroups have substantial differences in PFS, which improve current risk stratification models for Group 4 (REF.⁶²). A subset of low-risk patients with Group 4 MB with either chromosome 11 loss or 17 gain have an exceptionally favourable outcome, whereas standard-risk patients lacked either of these anomalies and high-risk patients lacked these features and had metastasis at diagnosis⁹⁴. Notably, these low-risk cytogenetic features are closely associated with Group 4_{Low-risk} suggesting a common underpinning molecular pathology (BOX 3).

Subtypes of Group 3 and Group 4

Although the current consensus on MB subgroups acknowledges the four-subgroup structure officially recognized by the WHO, as previously mentioned, intrasubgroup and intersubgroup heterogeneity has been reported.

More recent studies based on DNA methylation profiling have demonstrated the utility of annotating Group 3 and Group 4 samples together according to their underlying subtypes^{42,62}. In one study of 740 patients with Group 3 MB or Group 4 MB, eight unique subtypes were identified using DNA methylation array, including subtypes that were composed solely of patients with Group 3 or Group 4 MB, and subtypes that comprised a mixture of both patients with Group 3 MB and those with Group 4 MB⁴². Large, international consensus studies are underway to determine the most robust and logical solution for defining heterogeneity in Group 3 MB and Group 4 MB according to molecular subtypes. Future MB clinical trials are anticipated to stratify patients with Group 3 MB and Group 4 MB according to subtype, and current parental Group 3 and Group 4 subgroup definitions may be superseded by more specific subtype definitions.

Tumour microenvironment

The tumour microenvironment in MB has been studied incompletely and largely inferred on the basis of positivity for a modest number of a priori selected immune cell markers. Relative to other brain tumours, MBs appear to be profoundly immune evasive. Indeed, MBs are not significantly different from healthy brain tissue in terms of immune infiltrate, whereas other paediatric brain tumours such as pilocytic astrocytoma, glioblastoma and ependymoma have substantial immune cell infiltrates⁹⁵. More CD163-positive (M2-like) macrophages have been observed using immunolabelling in SHH-MB than in Group 4 MB tumours⁹⁶. In another study, T cell immunosuppressive marker programmed

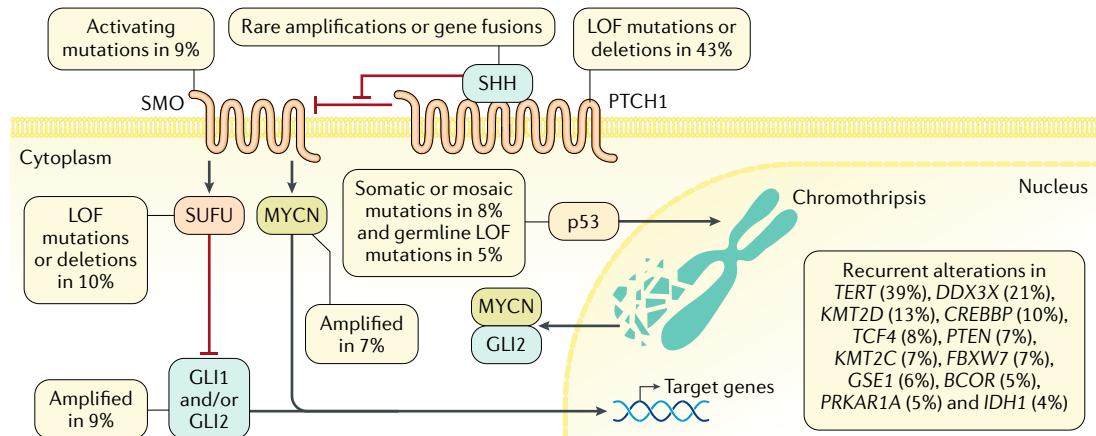


Fig. 5 | SHH subgroup. Genes of the canonical sonic hedgehog (SHH; ligand for the propagation of SHH signalling) signalling pathway are recurrently altered in patients with SHH-medulloblastoma (MB)⁴². GLI1 and GLI2 (glioma-associated oncogene homologues 1 and 2), essential transcription factors downstream of Hedgehog signalling; LOF, loss-of-function; MYCN, transcription factor downstream of Hedgehog signalling; p53 (tumour protein p53), transcription factor regulating diverse cellular processes through regulation of expression of target genes; PTCH1 (patched 1 homologue), receptor for secreted Hedgehog ligands; SMO (smoothened), receptor that is associated with PTCH1 and transduces Hedgehog signal; SUFU (suppressor of fused homologue), negative regulator of the Hedgehog signalling pathway. The percentage values denote the proportion of patients with SHH-MB who have the associated genetic mutation.

cell death 1 ligand 1 (PD-L1) expression was compared between different MB subgroups, revealing low expression across subgroups and rare instances of focal PD-L1 expression in a subset of SHH-MBs together with immune infiltration⁹⁷. In addition, SHH-MBs have been observed to have higher infiltration of tumour-associated macrophages (assessed using CD163 immunohistochemical staining) than Group 3 MBs or Group 4 MBs in another study⁹⁸. Finally, one study investigating publicly available expression array data sets from ~700 MBs identified low expression of immune markers overall, with modest differences in the quantity of infiltrates across subgroups⁹⁹. More systematic analyses of the MB microenvironment using single-cell sequencing and mass-spectrometry-based approaches are currently ongoing and will likely shed more light on these aspects.

Diagnosis, screening and prevention

The diagnosis of MB is based on clinical symptoms, MRI of the brain and total spine to assess the primary tumour and to screen for macroscopic metastases, CSF cytology to detect microscopic metastases, and an integrated histopathological and molecular analysis.

Clinical manifestations

Patients can initially present with nonspecific symptoms such as headaches, clumsiness, nausea or morning vomiting, fatigue or poor school performance, which might be due to hydrocephalus-related increased intracranial pressure or a direct effect of the tumour. These symptoms may be intermittent and subtle at first, evolving over a period of weeks to a few months. More specific symptoms of MB include ataxia, difficulties with handwriting or other motor skills and problems with vision or strabismus. In those with spinal metastases at diagnosis, the presenting symptoms can also include back

pain, gait difficulties and, rarely, neurogenic bladder and bowel dysfunction. Spinal metastasis is typically asymptomatic leptomeningeal seeding ('sugar-coating'). Owing to accelerated tumour growth, symptoms might rapidly worsen over time and lead to the initiation of diagnostic procedures including MRI of the brain and spinal cord. As the skull sutures are open for up to 18 months after birth, increased intracranial pressure in these young children may be compensated for by macrocephalus and prolonged oligosymptomatic intervals, leading to delayed diagnoses in a substantial subset of children¹⁰⁰.

Imaging, cytology and staging

Imaging is used to diagnose and stage MB and includes cranial and spinal MRI including contrast sequences (FIG. 8). CT scans are obsolete owing to the radiation burden and the excellent tissue resolution of MRI, with the exception of emergency situations. CSF cytology is routinely assessed at the time of diagnosis and is combined with imaging results to allow for the staging of MB. Staging is carried out using the Chang classification¹⁰¹, which defines macroscopic and microscopic metastases and stages patients into five groups, ranging from M0 to M4 (BOX 4). Metastasis can occur within the CNS or outside the cerebrospinal axis, although the latter is very rare. An examination of factors associated with the outcome of paediatric patients with MB treated in clinical trials shows the prognostic value of the Chang staging system. Interestingly, a recent publication by Garzia and colleagues shows very strong *in vivo* evidence for haematogenous spread in a parabiosis mouse model using human MB cells and re-homing of metastatic cells to the CNS¹⁰². This finding will potentially fundamentally change our previous understanding of metastasis formation in MB, although this requires further study.

Histopathology

The diagnosis of MB is impossible without a surgical specimen that is used for integrated histopathological and molecular analysis. The specimen is obtained at the time of surgical resection of the tumour (see Management, below). Histopathological and molecular analyses are essential for the diagnosis of MB as the posterior fossa is a common location for other paediatric brain tumours that are radiographically similar to MB, such as pilocytic astrocytoma, ependymoma, AT/RT and embryonal tumour with multi-layered rosettes. Traditionally, the diagnosis has been established by histopathological evaluation, and a total of five morphologies have been distinguished (FIG. 9): classic, desmoplastic/nodular (DN), MB with extensive nodularity (MBEN), large cell and anaplastic (the latter two were later combined into one histopathological category as LC/A)¹⁰³. Although these histological variants partially reflect underlying molecular heterogeneity, the most recent update of the WHO classification⁸ requires the combination of histologically defined and genetically defined variants in an integrated diagnosis as a standard, whenever technically possible.

All histological morphologies are found in SHH-MB tumours: classic has been reported in ~40–45% of tumours, DN in ~30–35% of tumours, MBEN in ~10% of tumours and LC/A in ~15–20% of tumours. The SHH molecular subgroup is further subdivided into SHH-TP53 wild-type tumours, which are commonly associated with DN histology (with DN almost invariably falling into the SHH-MB subgroup), and SHH-TP53 mutant tumours, which are often associated with LC/A morphology⁶⁴. Conversely, WNT-MBs are almost all of classic histology. Group 3 MBs are either classic or LC/A morphology, whereas most Group 4 MBs are of classic morphology, although ~10–15% present with LC/A morphology¹⁰⁴.

Molecular classification

DNA methylation profiling has superseded the use of gene expression analysis to identify MB subgroups and is considered the gold-standard method for determining MB subgroup status and substructure within subgroups (subtypes)^{105,106}. Array-based methylation analysis, transcriptome sequencing, array-based RNA expression analysis, nanoString or a minimal methylation classifier¹⁰⁷ assay can all be used for reliable MB subgroup identification^{64,108}. In addition, immunohistochemistry-based assays can be used to discriminate WNT-MB and SHH-MB from non-WNT/non-SHH MBs¹⁰⁹.

Assigning patients to the WNT-MB subgroup involves a combination of *CTNNB1* exon 3 sequencing, chromosome 6 copy-number assessment and/or immunohistochemistry for nucleopositive β-catenin. However, none of these methods can conclusively determine WNT-MB subgroup status; thus, combining these tests with DNA methylation-based or expression-based approaches is recommended^{110,111}. As previously mentioned, SHH-MBs are often characterized by DN or MBEN histology and can be reliably detected using immunohistochemistry-based assays¹⁰⁹ or using the genetic analyses described above. Assessment of *TP53* mutation status is important for patient stratification,

as these mutations are associated with a very poor prognosis when found in patients with SHH-MB. As most patients with MB and hereditary predisposition have SHH-MB, performing a minimal mutational analysis in tumour and blood for *PTCH1*, *SUFU* and *TP53* for all patients with SHH-MB is generally recommended¹⁹. Group 3 MBs and Group 4 MBs can be reliably distinguished only using DNA methylation-based or expression-based approaches. The presence or absence of *MYC* or *MYCN* amplification may further add to patient stratification within Group 3 MB^{2,94}.

Differential diagnosis

As previously discussed, molecular tests and immunohistochemistry can be used to reliably distinguish MBs from other neuronal and embryonal brain tumours with a similar histopathology, such as AT/RT, embryonal tumour with multi-layered rosettes, small-cell glioblastoma and posterior fossa ependymoma. The defining molecular feature of AT/RT is *SMARCB1* or *SMARCA4* loss-of-function, which can be screened for using *SMARCB1* and *SMARCA4* immunohistochemistry, respectively¹¹². Embryonal tumours with multi-layered rosettes are defined by an amplification of a microRNA cluster on chromosome 19 and robust immunopositivity for *LIN28A*^{113–116}, which, when present, excludes the diagnosis of MB. Glioblastomas and MBs have different patterns of GFAP (a marker of glial cells) immunoreactivity. In addition, glioblastomas often harbour very characteristic genetic aberrations (for example *H3F3A* and *HIST1H3B* mutations or amplifications and/or mutations in *PDGFRA* and other receptor tyrosine kinases) that are exceedingly rare in MB. Posterior fossa ependymoma group A is typically characterized by a

Box 3 | Clinical risk categories of MB

Very-low-risk

- WNT M0
- Low-risk
- WNT M⁺
- SHH, MBEN
- iSHH, subtype II (?)
- Group4_{Low-risk} (?)

Intermediate-risk

- SHH, TP53 WT
- SHH, non-MBEN
- Group 4 others (?)

High-risk

- Group 3, non-MYC amplified
- iSHH, subtype I (?)
- Group4_{High-risk} (?)

Very-high-risk

- SHH, TP53 mutant
- Group 3, MYC amplified
- Group 3, M⁺

iSHH, infant SHH-MB; M0, non-metastatic at diagnosis;

M⁺, metastatic at diagnosis; MB, medulloblastoma; MBEN, MB with extensive nodularity; SHH, sonic hedgehog; WT, wild-type.

global loss of histone H3 lysine 27 (H3K27) trimethylation, which can be assessed using immunohistochemistry¹¹⁷. A more recent approach to exclude these and other rarer diagnoses uses DNA methylation fingerprints for brain tumour classification, including assessment of molecular subgroups and copy-number aberrations^{105,118}.

Screening

Screening programmes to allow for early MB detection are useful in patients with Gorlin syndrome and Li-Fraumeni syndrome as published in guidelines of the American Association for Cancer Research (AACR) Cancer Predisposition Working Group^{119,120}. Whether brain tumour screening is beneficial for carriers of germline *APC*, *BRCA2* or *PALB2* mutations, which occur in some patients with MB¹⁹, is currently not well established. On the basis of a large-scale study investigating hereditary predisposition to MB, all patients with SHH-MB, as well as patients with WNT-MB lacking somatic *CTNNB1* mutation, should be offered genetic testing and counselling owing to the high prevalence of germline mutations in these patients¹⁹.

Management

Maximal surgical resection followed by risk-adapted CSI and adjuvant chemotherapy have produced the best survival for MB (FIG. 10). With this therapy, the estimated

5-year overall survival is ~80% for non-infants with non-metastatic GTR (when no residual tumour can be visualized by MRI) and ~60% for children with metastatic MB and/or STR (defined as leaving >1.5 cm² of residual tumour)^{9,11,121,122}. These estimates have been stable for the past two decades and, except for some minor variations between protocols, this management is the accepted standard of care for MB.

Although the survival of MB is, in general, quite high, there are some caveats and drawbacks that argue for continuous adaptations of this treatment strategy. First, this therapeutic strategy has a high toxicity rate (see Quality of life), which needs to be adjusted and reduced whenever possible. Second, the treatment-associated adverse effects of CSI increase inversely with younger age and are considered to be too neuropsychologically debilitating to be acceptable for infants (patients <3 years of age). Consequently, treatment strategies delaying or avoiding CSI have been sought in young patients, often resulting in an inferior survival compared with patients who received conventional treatment. Finally, the observations that patients with different subgroups and subtypes of MB who received identical therapies had predictably and reproducibly divergent outcomes has created an opportunity to improve risk-adapted models of therapy, such that toxicity can be reduced when appropriate and survival maintained and even improved.

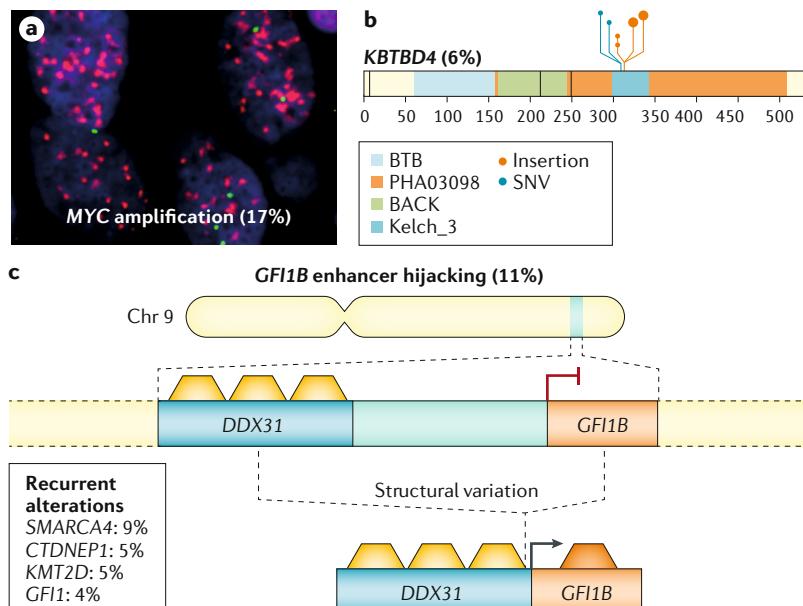


Fig. 6 | Group 3. Summary of prevalent somatic alterations in Group 3 medulloblastoma (MB). Alteration frequencies are derived from REF.⁴². **a** | Fluorescence in situ hybridization (FISH) of a MB sample harbouring high-level MYC amplification. **b** | Hotspot somatic mutations in *KBTBD4*. Lollipop symbols indicate the clustered positions of recurrent mutations seen in patients with Group 3 MB. **c** | Schematic depicts recurrent structural variants on chromosome 9q that position highly active enhancers present in *DDX31* proximal to *GFI1B*, leading to *GFI1B* overexpression (enhancer hijacking). *DDX31*, encodes DEAD-box helicase 31, protein of unknown function; *GFI1B*, encodes growth factor independent 1B, transcription factor involved in development and differentiation of haematopoietic lineage; *KBTBD4*, encodes Kelch repeat and BTB domain containing 4, protein of unknown function; *MYC*, encodes proto-oncogene c-Myc, which has an integral role in cell cycle progression, apoptosis and cellular transformation; SNV, single-nucleotide variant.

Types of treatment

Surgery. Surgery has a critical role in the management of MB. Ideally, GTR of the tumour should be carried out at initial diagnosis, before adjuvant radiotherapy or chemotherapy. The extent of surgical resection remains a prognostic factor even in the molecular era, as STR is consistently associated with a worse outcome compared with GTR or near-total resection (NTR; <1.5 cm² residual tumour)^{123,124}. Secondary surgeries to remove residual tumours should be considered when possible. However, recent data support a concept whereby patients after total resection (GTR or NTR) share the same prognosis; thus, overambitious resection of a small residual tumour covering the brainstem should be avoided given the high risk of cerebellar mutism following surgical resection of MB and when damage to high-risk structures (such as cranial nerves and brainstem) precludes complete resection^{124–127}. Thus, the overarching and current goals of surgery are tissue procurement for histopathological analysis and molecular diagnosis, and maximal safe cytoreduction. Indeed, as molecular diagnosis is a determinant of risk stratification, procuring tissue for accurate treatment planning and management is essential^{128,129}.

Radiation. Owing to the propensity of MB to metastasize within the CNS, the most successful radiation approach has involved irradiation of the entire crano-spinal axis (for example, CSI) with a focal boost to the primary tumour site. Before the use of CSI, MB was incurable in older children¹³⁰, and whenever CSI dose has been reduced or omitted, outcomes have, in general, been inferior^{131,132}. However, owing to the severe,

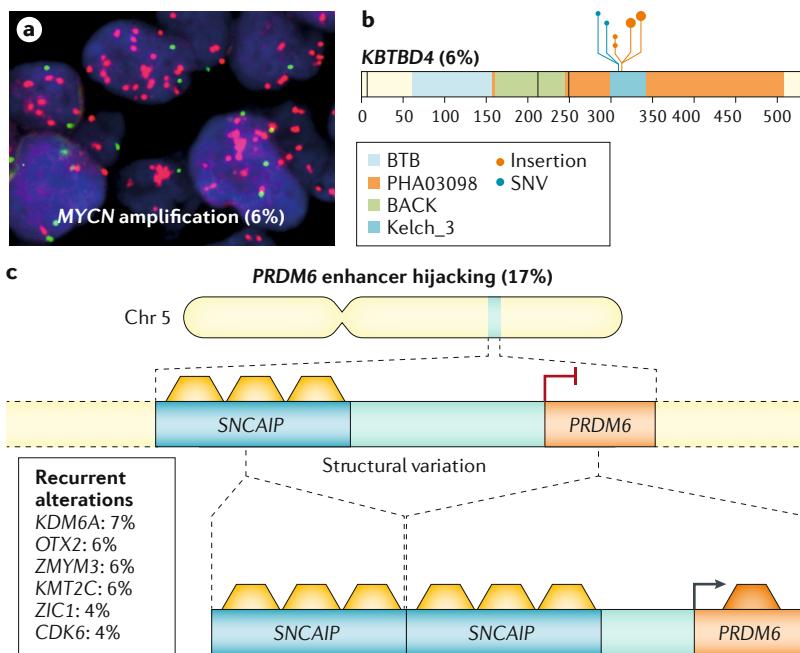


Fig. 7 | Group 4. Summary of prevalent somatic alterations in Group 4 medulloblastoma (MB). Alteration frequencies are derived from REF.⁴². **a** | Fluorescence in situ hybridization (FISH) performed on a MB sample harbouring high-level amplification of MYCN. **b** | Hotspot somatic mutations in *KBTBD4*. The lollipop symbols indicate the clustered positions of recurrent mutations seen in patients with Group 4 MB. **c** | Schematic depicts recurrent structural variants on chromosome 5q that reposition highly active enhancers present in *SNCAIP* proximal to *PRDM6*, leading to *PRDM6* expression. *KBTBD4*, encodes Kelch repeat and BTB domain containing 4, protein of unknown function; *MYCN*, encodes neuroblastoma MYC oncogene, basic helix-loop-helix (bHLH) domain transcription factor; *PRDM6*, encodes PR/SET domain 6, PR/SET domain-containing transcriptional repressor with potential histone methyltransferase activity; *SNCAIP*, encodes synuclein- α interacting protein, interacting partner of α -synuclein in neuronal tissue; *SNV*, single-nucleotide variant.

widespread adverse effects of CSI, such as permanent neurocognitive disability, neuroendocrine dysfunction, growth disturbances, infertility, growth deformities and secondary malignancy, efforts to reduce, defer or omit radiation therapy have been consistently tried and proposed, particularly in children <3–5 years of age. Although dose reductions have often failed, modifications in the delivery of radiation, such as the use of intensity-modulated radiation therapy and conformal 3D photon therapy, have minimized unintentional tissue overexposure and non-target tissue exposure while preserving adequate target distribution and outcomes¹³³. Furthermore, a steady reduction in the boost margin (from the entire posterior fossa, to a 2 cm margin around the tumour bed¹³⁴, to a 1 cm margin (NCT00085202 and NCT00085735)¹³⁵, to a 0.5 cm margin (NCT01878617 and NCT02066220)) has substantially reduced the field of high-dose radiation without demonstrating any negative effect, as yet, on survival. Proton beam radiation therapy is another modality with a lower entrance dose and no exit dose, thereby increasing the potential to conform treatment to only the target structures, with sparing of non-target tissues^{132,136}. Results from early publications using proton beam radiation therapy are encouraging as no evidence suggests an inferior outcome after treatment, and some data suggest lower toxicity profiles^{136–138}.

However, direct comparisons of photon therapy and proton radiotherapy are lacking given different cohorts, boost volumes and therapy, and larger prospective or even randomized trials are needed. Furthermore, the toxicity of these new modalities needs to be carefully evaluated before newer therapy replaces the use of current therapies^{139–141}.

Adjuvant chemotherapy. Multi-agent chemotherapy was originally added to MB management in the 1970s as a means to increase survival¹⁴² and in the 1990s as a means to offset the inferior survival outcomes brought about by reducing the CSI dose in patients with non-metastatic MB from 36.0 Gy to 23.4 Gy (REF.¹³²). Indeed, over the following years, chemotherapy has proved to be a valuable adjunct to surgery and radiation therapy and has substantially contributed to increased survival in those with metastatic and non-metastatic disease^{9,11}. Collectively, numerous studies have demonstrated the survival benefit of post-radiation chemotherapy over pre-radiation chemotherapy in patients with non-metastatic MB^{143,144}, and the most widely used chemotherapeutic agents are cisplatin, carboplatin, vincristine, cyclophosphamide and lomustine. Combinations of these drugs in cycles of multi-agent chemotherapy have been implemented empirically, usually without prior phase I or II testing of single chemotherapeutic drugs. New chemotherapy agents have rarely been incorporated into the most common front-line MB management and, disconcertingly, the dose and number of courses across different treatment regimens remain highly variable. The goal of chemotherapy is similar to that of radiation therapy — that is, to deliver the minimum required dose to reach maximal disease control using the least toxic agents.

The current convention

For the two-thirds of patients with MB who are between 3 and 18 years of age, who present without metastatic disease and achieve at least an NTR after surgical resection, postoperative therapy includes 23.4 Gy CSI with a 54.0 Gy primary tumour bed boost (in some regimens together with concurrent vincristine chemotherapy) followed by 4–9 cycles of vincristine, cisplatin, cyclophosphamide or lomustine chemotherapy; 5-year survival is ~80%^{9,11,122}. Prolonged delay in CSI in this standard-risk setting has typically been associated with inferior outcomes^{143,145}. For the remaining patients who present with metastatic disease, or who have STR after surgery, postoperative therapy includes 36.0 Gy CSI with a 54.0 Gy boost to the primary tumour and a 50.0–54.0 Gy boost to bulky sites of metastatic disease followed by 4–9 cycles of vincristine, cisplatin, carboplatin or cyclophosphamide in North America. Most European regimens use upfront chemotherapy followed by conventional (for example, one dose of 1.6–1.8 Gy per day) or hyperfractionated radiotherapy with and without acceleration (for example, two doses of 1.3 Gy per day or two doses of 1.0 Gy per day). In addition, regimens using carboplatin concurrent with radiotherapy as radiosensitizers or intraventricular chemotherapy with methotrexate have been investigated with positive results^{9,13,121},

although the optimal combination of available treatment elements needs to be clarified. In contrast to non-metastatic MB, no gold-standard sequence exists for adjuvant treatment in metastatic MB, as similar survival (~60% at 5 years) has been obtained by both strategies^{9,13,121}.

Success is limited for young infants (0–1 years of age) and older infants or young children (1–5 years of age) with MB, and there is little agreement on the best management strategy for these patients. All trials have attempted to omit, reduce or, at least, defer CSI owing to the damaging effect of this treatment on the developing brain. Systemic high-dose chemotherapy

and intrathecal methotrexate have been adopted from leukaemia therapy as a surrogate for CSI^{146,147}. Some European and North American regimens used intravenous and/or intraventricular methotrexate, whereas other regimens did not incorporate methotrexate treatment by either route. High-dose myeloablative chemotherapy regimens have also been used to overcome the need for CSI in some regimens¹⁴⁸. A retrospective analysis on the use of a myelosuppressive rather than myeloablative sequential high-dose chemotherapy regimen demonstrated promising results¹⁴⁹. In addition, focal radiation has been used between chemotherapy regimens to evaluate the effect of partial irradiation¹³¹.

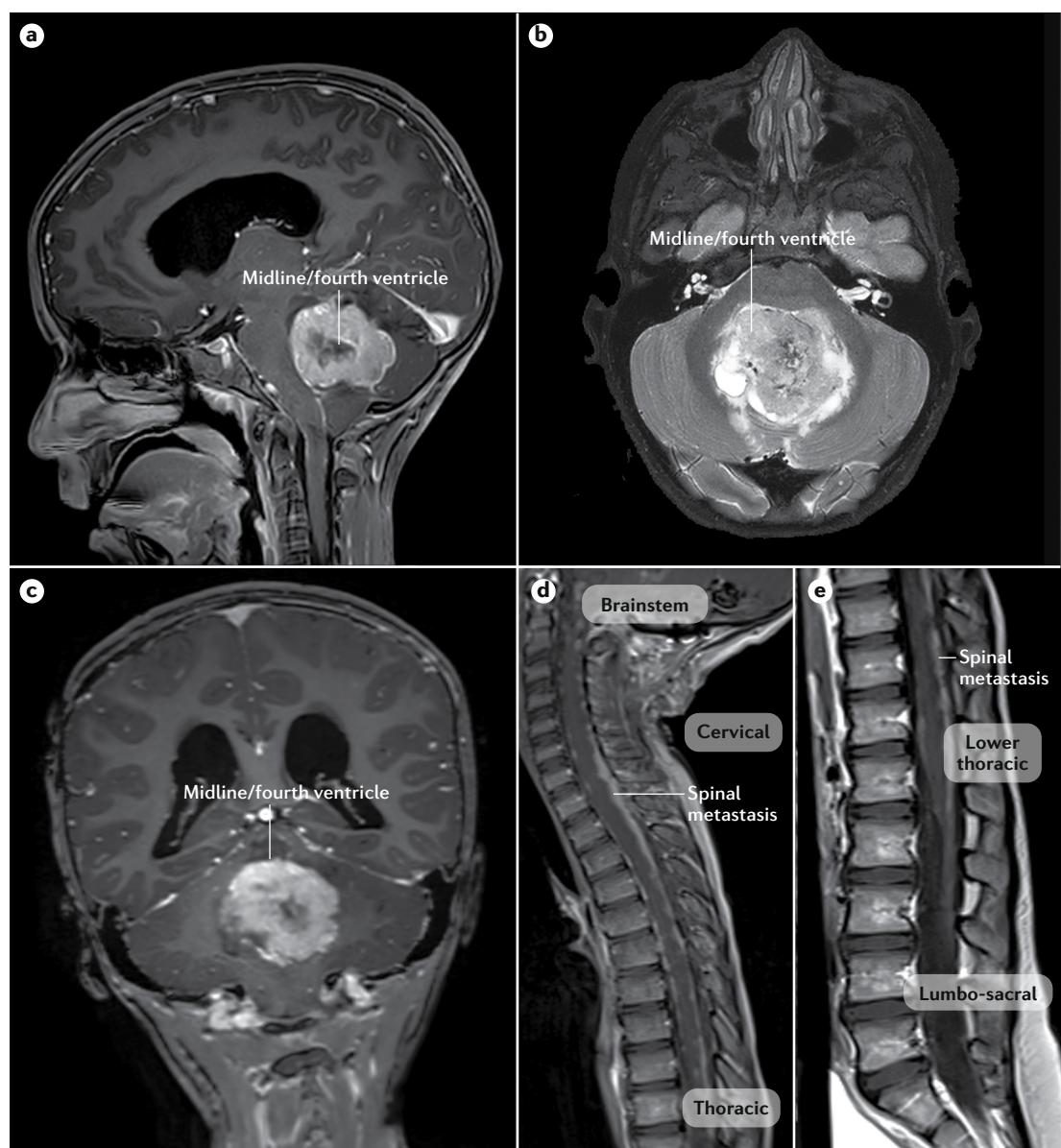


Fig. 8 | MRI of MB. **a–c** | Cranial MRI images of a patient with medulloblastoma (MB). Sagittal plane (part a), transverse plane (part b) and coronal plane (part c) are shown. **d,e** | Spinal MRI of patient after suboccipital craniotomy for tumour in the posterior fossa with multiple enhancing metastatic lesions within the spinal canal. These lesions indent the lower thoracic spinal cord and occupy much of the caudal thecal sac. Leptomeningeal disease is also present as streaks of white ‘sugar-coating’ outlining the cord and best seen along the anterior portion of the brainstem, lower cervical and lower thoracic cord.

Despite these approaches, the survival of patients <5 years of age with MB has remained inferior to that for older children treated with CSI⁶³. However, these approaches have begun to identify histopathological and molecular subsets of MB that may respond well to this therapy^{63,147,150}. For example, high relapse-free survival (up to 90%) has been reported for both high-dose chemotherapy and intrathecal methotrexate in young children with histological or biological low-risk features (such as those with desmoplastic SHH-MB). However, a direct comparison of both strategies in terms of survival, toxicities and late effects has not yet been performed. A subset of young children with a biological low-risk profile (those with iSHH-II) might be successfully treated by conventional chemotherapy alone, whereas those with iSHH-I might require more intensive approaches⁶³. Young children with metastatic disease or non-favourable histological or biological features (such as those with Group 3, Group 4, classic or LC/A MB) are considered high-risk patients. Intensive chemotherapy regimens including myeloablative chemotherapy or intrathecal methotrexate have led to sustained tumour control without CSI only in a minority of patients, and development of new, effective and tolerable strategies is urgently required for this group of patients.

MB is very rare in adults but can still occur. Owing to the improved tolerability of CSI in adults, the use of chemotherapy in this population has lagged behind the paediatric experience. However, some studies have shown that the benefit of adjuvant chemotherapy is not likely restricted to paediatric patients and suggest that adjuvant chemotherapy should be added to CSI as standard treatment for adults with MB^{151–154}. However, clinical trials that include adults are still needed to define the optimum management of this population.

If MB recurs after upfront (initial) therapy, the prognosis is very poor, with 5-year survival after relapse of <10%, even for initial standard-risk patients^{155,156}, except in patients (for example, young children) who have not received CSI. Although some of these patients might be successfully salvaged with CSI, they will still have a high morbidity as a consequence of treatment. Initial studies of MB at relapse have revealed substantially different disease characteristics compared with at diagnosis. For example, clear evidence of tumour clonal evolution, the acquisition of high-risk clinical features and specific molecular events (such as, combined *MYC* or *MYCN* amplification and *TP53* mutation) have been reported^{157,158}. Early-phase trials that evaluate molecularly guided therapies, on the basis of biopsy and assessment of disease characteristics at relapse, are recommended to develop improved treatments at relapse and owing to how these approaches could inform upfront therapy.

Incorporating molecular risk into clinical management. A major obstacle to defining maximally curative and minimally toxic treatment of MB has been the continued management of MB as a uniform disease. Instead, what is needed is a management plan that ascribes differential therapy to different risk groups on the basis of molecular and clinical risk features (BOXES 2,3).

Box 4 | Chang staging system

- M0 — tumours show no evidence of metastasis in MRI studies and cerebrospinal fluid (CSF) cytological studies.
- M1 — microscopic tumour cells are detected in CSF cytology preparations.
- M2 — intracranial metastatic deposits can be observed beyond the primary site (in cerebellar or cerebral subarachnoid space or in third or lateral ventricle) using MRI.
- M3 — metastatic deposits in the spinal subarachnoid space.
- M4 — metastasis outside the cerebrospinal axis.

When the histological variants and subgroups of MB are taken into account in large retrospective and clinical trial cohorts, the differential response to therapy has superseded the differences between trial designs. That is to say, as long as the general approach of maximal safe surgery, CSI and adjuvant chemotherapy has been followed in patients with non-metastatic MB, the 5-year PFS of those with WNT-MB has remained excellent (>95%), of those with Group 3 MB poor (~50–60%) and of those with SHH-MB or Group 4 MB intermediate (~70–80%)⁶⁸. In addition, differential responses to therapy have also been noted in infants, in whom those with SHH-MB (or by surrogate having DN/MBEN pathology, which are all SHH-MB) benefit from the radiotherapy-sparing, chemotherapy-only approach⁶³. Moreover, patients with SHH-TP53 mutant MB have a very poor prognosis, and patients with some Group 4 MB subtypes (for example, Group 4_{Low-risk} or patients with either chromosome 11 loss or chromosome 17 gain) have a very good prognosis^{62,67,68,94} (BOX 5).

The histopathological variants of MB are associated with different outcomes; patients with LC/A MBs have a poor outcome compared with those with classic tumours in clinical trial cohorts^{159,160}, and some studies have shown a better prognosis for individuals with DN MBs, particularly MBENs^{150,161}. Risk stratification schemes that incorporate histopathological variant stratification have been proposed and tested retrospectively in trial cohorts^{106,162}, but how to combine information on histopathological variants and molecular group or alterations for the optimal treatment of patients with MB is still to be determined. Some ongoing trials are addressing this issue; for example, in the SJMB12 trial, diagnosis of the LC/A variant is used alongside *MYC*/*MYCN* status to influence clinical risk and stratification in those with non-WNT, non-SHH-MBs (NCT01878617).

Collectively, the improved prognostication and treatment stratification that molecular testing allows also promises a new era of MB management that is already underway. The major and immediate clinical effect is the opportunity to tailor therapy according to the risk of relapse. For example, judicious dose reductions of conventional therapy can be explored in patients with the lowest risk of relapse (such as those with WNT-MB) to reduce treatment-related morbidities. In addition, patients with the highest biological risk of relapse who were previously classified as having lower-risk disease

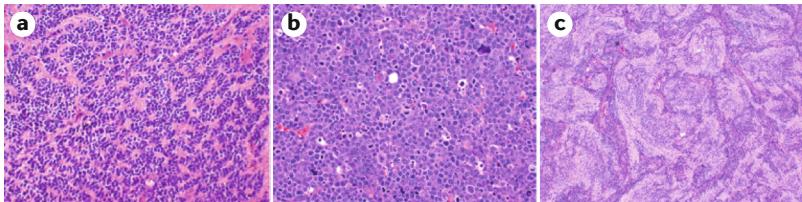


Fig. 9 | Histopathology. **a** | The classic medulloblastoma (MB) consists of undifferentiated small cells in a sheet-like pattern with mild to moderate nuclear pleomorphism (magnification $\times 200$). **b** | The large cell/anaplastic MB exhibits marked nuclear pleomorphism accompanied by a high mitotic count and abundant apoptosis, cell wrapping, a large cell phenotype and further features (magnification $\times 400$). **c** | Desmoplastic/nodular MBs demonstrate nodules of neurocytic cells and internodal desmoplasia around embryonal cells showing variable nuclear pleomorphism. The MB with extensive nodularity (shown in part **c**) is a desmoplastic/nodular variant with large irregular regions of neurocytic cells against a neuropil-like matrix (magnification $\times 100$).

can have their treatment escalated. Finally, for patients who are predicted to relapse on maximal conventional therapy, modifications to therapy can be applied or alternative strategies devised and pursued. This approach focuses de-escalation strategies on low-risk patients, preserves average-risk patients from risky de-escalation or unnecessary augmentation in therapy and effectively targets poor responders for novel therapies. Current trials that have taken this approach are the SJMB12 (NCT01878617), PNET5 (NCT02066220) and ACNS1422 (NCT02724579) trials. All offer reduced-dose CSI to patients with WNT-MB (15.0 Gy or 18.0 Gy). In the de-escalation trial within the PNET5 study, children with WNT-MB < 16 years of age at diagnosis can be included if they have no metastases and the tumour has achieved NTR. In addition, the PNET5 study is also investigating the simultaneous application of carboplatin with radiotherapy in patients with non-WNT/non-high-risk (that is, non-metastatic, no molecular or histopathological high-risk features) MB, and includes an interventional study assessing the use of reduced alkylator-containing chemotherapy and risk-adapted radiotherapy for children with MB and *TP53* germline mutations (individuals with Li-Fraumeni syndrome), aiming to compromise between tumour control and avoidance of further increasing the high risks for secondary malignancies. The SJMB12 study is investigating the tolerability and effect on survival of adding gemcitabine and pemetrexed cycles to the conventional treatment for those with high risk Group 3 MBs or Group 4 MBs on the basis of promising preclinical work in animal models¹⁶³. In addition, SJMB12 is evaluating the tolerability and effect on survival of adding targeted SHH inhibitor therapy to skeletally mature patients with SHH-MB⁷⁴.

Changes to conventional MB therapy, no matter how small, could benefit patients by reducing toxicity or could negatively affect patients by reducing disease control or generating unanticipated toxicity. Indeed, de-escalation in the COG ACNS0331 trial led to an unacceptable recurrence rate in children with average-risk MB who received 18.0 Gy CSI¹⁶⁴. Thus, a meticulous, rigorous and careful clinical trial approach should guide all therapeutic modifications such that new risk-adapted models can be explored but halted if detrimental. Given all the new

insights molecular technology has already brought and continues to bring to the field, medical management of MB in the molecular era has only just begun.

Quality of life

Survivors of paediatric MB have an increased risk of poor quality of life owing to the adverse effects of MB and its treatment on brain development, including effects of the tumour (such as mass effect or hydrocephalus), surgery, chemotherapy and CSI^{165,166}. Physical, neurological and neuropsychological disabilities can manifest acutely following treatment and persist into adulthood in these patients^{135,167,168}. A reduction in intelligence is perhaps the most pressing concern^{169,170}. Deficits in speed of processing, attention, memory and executive function are observed in patients who received surgery alone as well as in those who received surgery, chemotherapy and CSI^{171–175}. The cerebellar location of the tumours and the surgery can lead to motor and behavioural impairments, with the most profound constellation of symptoms characterized as cerebellar mutism syndrome (CMS)¹⁷⁶. CMS is more frequently observed in patients with MB than in those with other cerebellar tumours, and its presence predicts neuropsychological impairment^{127,177}. Preoperative risk stratification for CMS using MRI is emerging as a viable strategy for mitigating adverse effects: risk factors for CMS include the tumour location, pattern of invasion or compression in the cerebellum and older age. Preoperative evaluation of these factors might influence strategies for surgical treatment of cerebellar tumours¹⁷⁸.

CSI is associated with substantial neurotoxicity, including white matter damage and decreased hippocampal volume, and this toxicity predicts deficits in neuropsychological function^{173,179,180}. Animal and human histological studies have demonstrated injury to endothelial cells of the microvasculature of the brain¹⁸¹ and damage to neural stem cells after radiation^{182–184}. White matter damage and hippocampal volume loss following CSI are robust predictors of reduced speed of processing and poor memory function, respectively^{173,174,180,185}. Recent longitudinal neuroimaging studies support the presence of early acute and stable injury after CSI^{173,186}, which raises the possibility of early intervention to mitigate damage. Younger age, higher radiation doses, larger treatment volumes and specific germline genetic markers (that is, *GST* polymorphisms) predict increased neuropsychological morbidity^{169,187–190}.

Modern treatment approaches hold promise for decreasing neurotoxicity; for example, treatment with reduced-dose CSI and targeted boost to the tumour bed ameliorates poor intellectual outcome and white matter damage^{135,179}. In addition, hyperfractionated radiation has shown possible benefit for specific cognitive functions, although with no effect on overall intelligence^{191,192}. Proton beam radiation reduces the dose to healthy brain tissue, and some retrospective evidence suggests that this modality might moderate intellectual impairment^{138,193–195}. However, a sparing of cognitive functioning cannot be expected either by protons or photons in patients with MB treated with a given CSI dose, which always includes the entire brain. Specific

cognitive deficits, such as reduced speed of processing, continue to be observed following all forms of radiation^{135,193}. Although the use of postoperative chemotherapy with radiation avoidance or delay in young children with MB mitigates neuropsychological impairment, such a strategy should be informed by MB subtype^{147,196}. When quality of life and intelligence are evaluated on a subgroup-specific basis, patients with SHH-MB have better outcomes than other subgroups despite poor survival^{197,198}. Patients with WNT-MB or Group 4 MB benefit most from limiting radiation exposure, showing stable intellectual trajectory following treatment with reduced-dose radiation and limiting the boost to the tumour bed¹⁹⁸.

Finally, new clinical trials that target cognitive restoration and brain repair are emerging. Computerized training might improve working memory skills in children treated for MB¹⁹⁹, and physical exercise has shown some efficacy for normalizing white matter and hippocampal volume and improving processing speed²⁰⁰. Despite the substantial neurotoxicity associated with MB and treatment, there is now new hope that incorporation of strategies that mitigate early injury, therapy de-escalation based on subtype, novel radiation approaches and cognitive restoration strategies will substantially improve long-term quality of life in these patients.

Secondary malignancy

The exact proportion and spectrum of secondary malignancies after radiotherapy and chemotherapy for MB remain to be established, especially because until very recently it was standard practice not to re-biopsy most patients at relapse. Absence of biopsy tissue at this point makes it challenging to distinguish secondary malignancy in the area of highest exposure to radiotherapy from MB relapse. Evidence from prospective, nearly population-based diagnostic studies suggests that, especially in cases of clinically suspected local relapses of sporadic MB, after a certain latency (>36 months after primary diagnosis) the proportion of secondary glioblastomas can be substantial (DRKS00007623 and NCT02613962). To what extent this is linked to the focal radiation boost needs to be further analysed. The likelihood of developing secondary malignancies after intensive pretreatment at the time of primary diagnosis is even higher in patients with underlying cancer predisposition, such as haematological malignancies, sarcomas and glioblastoma (among others) in patients with Li-Fraumeni syndrome; gastrointestinal tumours in patients with APC germline mutations (that is, individuals with FAP syndrome); and basal cell carcinomas in patients with Gorlin syndrome¹⁹. However, on the basis of the lack of a standard re-biopsy at the time of

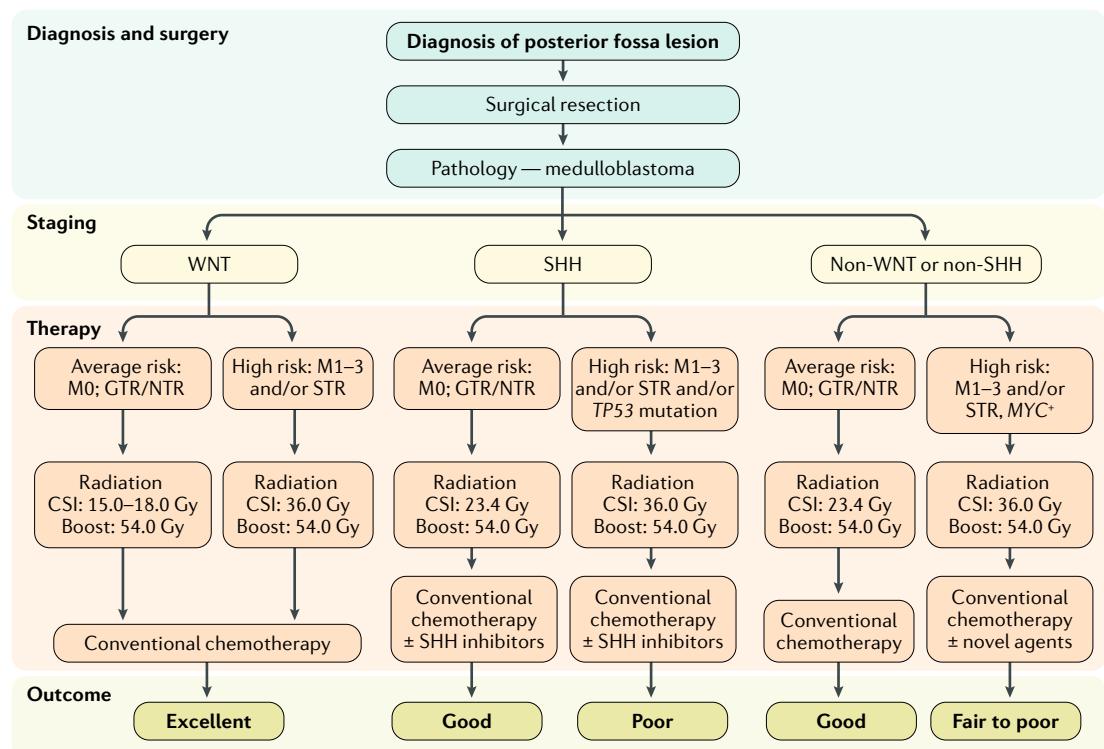


Fig. 10 | Current molecular risk-adapted management algorithm. The most recent clinical trials in medulloblastoma (MB) have incorporated molecular risk stratification into the trial design. At diagnosis, patients undergo maximal safe tumour resection, staging using cranial and spinal MRI and lumbar cerebrospinal fluid cytology to evaluate for metastatic disease. After neuropathological and biological tumour assessments, patients are stratified to risk-adapted postoperative therapy. Patients with average-risk WNT-MB receive de-escalations of crano-spinal irradiation (CSI), whereas post-pubertal patients with sonic hedgehog (SHH)-MB may receive SHH inhibitors. Patients with Group 3 MB or Group 4 MB (that is, high-risk, non-WNT, non-SHH tumours) receive more intensive subgroup-directed therapies, which might include novel agents. Conventional chemotherapy refers to multi-agent non-myeloablative systemic (intravenous) regimens. GTR, gross total resection; NTR, near-total resection; STR, subtotal resection.

Box 5 | Prognosis

For prognostication, histopathological variants and clinical features (age, metastatic disease and/or incomplete surgical resection) as well as subgroups and specific genetic changes have been implicated and validated in predicting outcomes¹⁶². Infants with tumours of desmoplastic/nodular (DN) or medulloblastoma (MB) with extensive nodularity (MBEN) histology typically are SHH-TP53 wild-type and are associated with favourable outcomes, even when treated with chemotherapy-only protocols that spare cranio-spinal irradiation (CSI)^{147,150,161}. Large cell/anaplastic variants comprise ~10% of cases and are associated with poor outcomes^{159,232}.

In non-infants treated with conventional multi-modal therapy, children with WNT-MB (<16 years of age at diagnosis) have a particularly favourable prognosis when treated using modern treatment protocols, and careful reduction in therapy intensity is currently being tested in clinical trials; however, applicability in older patients is not as clear^{209,211,233}. SHH-MBs with TP53 mutations comprise a very-high-risk subgroup, even when treated very intensively^{62,67}. At this stage, it remains unclear whether this holds true for both Li-Fraumeni-syndrome-associated tumours with germline TP53 mutations and seemingly sporadic SHH-TP53 MB in which TP53 mutations are not detectable in the patient's blood^{42,64}. Patients with Group 3 MB, especially those with MYC-amplified tumours and/or LCA histology, also have a dismal outcome as validated across multiple prospective trial cohorts^{58,111,211}, whereas patients with Group 4 MBs tend to have a more favourable outcome⁹⁴.

On the basis of these extensive biological, phenotypic and prognostic differences, it is of paramount importance to routinely and reliably detect MB subgroups, complemented with validated molecular genetic biomarkers in a clinical setting, and to consider them as stratifying biomarkers for future clinical trial design.

suspected relapse, there is most likely still a substantial under-reporting of secondary neoplasms overall²⁰¹.

Outlook

Overall, tremendous progress has been made over the past decade in understanding the biology of MB. This new knowledge is starting to be translated into a direct benefit for the patients in several ways, such as the application of state-of-the-art molecular diagnostics to both the tumour and germ line in routine clinical work-up and considering patients with cancer predisposition to present a separate challenge that requires special attention despite their fairly small numbers. In addition, stratification algorithms should be adjusted to include biological subgroups and clinically meaningful histopathological features, and clinical trials should test promising novel treatment concepts in carefully selected patient cohorts both at relapse and in the treatment-naïve setting. Finally, tumour evolution and heterogeneity should be taken into account when treating relapsed patients (which calls for routine re-biopsy at the time of relapse whenever possible), and efforts to learn from every patient (that is, reverse translation) should be increased.

Molecular classification

The 2016 WHO classification update for MB laid the foundation for the routine assessment of molecular subgroups of MB, including SHH-TP53 wild-type and SHH-TP53 mutant⁸. If subgroups are identified on the basis of DNA methylation analysis, DNA copy-number inferences can be extracted from the same data. Otherwise, identifying prototypic chromosome aberrations on the basis of the subgroup affiliation is clinically informative, including MYC amplification status in patients with Group 3 MB, MYCN and/or GLI2 amplification in SHH-MB, chromosome

17 aberrations in SHH-MB and Group 4 MB and monosomy 6 in WNT-MB, as these chromosomal alterations have been shown to be prognostic in specific subgroups⁹⁴. In addition, new guidelines have been proposed to assess a minimum of six genes for pathogenetic germline mutations, again dependent on patient subgroup status¹⁹.

Management

CSI still has an important role for most patients with MB. Modern radiotherapy approaches help to reduce the adverse effects that are attributed to radiotherapy. However, a randomized comparison between photon and proton radiotherapy for MB is still lacking, and the observation of secondary malignancies, mainly high-grade gliomas, occurring in the boost region in a proportion of patients certainly warrants careful analysis of the underlying causes²⁰¹.

In addition, the optimal use of the different chemotherapy regimens still needs to be determined. The efficacy of these treatments needs to be balanced against the associated treatment-related late adverse effects. The planned European prospective trial YC-MB for young children with MB is designed to investigate the efficacy of systemic chemotherapy and intraventricular methotrexate (full HIT-SKK regimen) in children with iSHH-I and a randomized de-escalation of intraventricular methotrexate for young children with iSHH-II (all children receive the systemic HIT-SKK chemotherapy backbone). In addition, this trial will evaluate the efficacy of an intensified systemic induction chemotherapy using a randomized comparison of two different high-dose chemotherapy regimens followed by maintenance therapy for young high-risk patients.

Incorporating subgroups into management. Although clinical trials with strict stopping rules to reduce treatment intensity for patients with proven WNT-MB are ongoing both in Europe and North America (NCT02066220, NCT01878617, NCT02212574 and NCT02724579), and MYC amplification as well as metastatic disease are uniformly regarded as high-risk features, only one ongoing study is currently stratifying patients on the basis of the remaining molecular subgroups (NCT01878617) and adding an SMO inhibitor to the standard treatment for patients with SHH-MB. The next steps could include an adolescent and adult MB trial that stratifies patients according to subgroups and includes an SMO inhibitor upfront (which is currently being planned in a trans-Atlantic setting) for patients with SHH-MB and careful treatment reduction for patients with Group 4 MB who have additional low-risk features. Additional strong preclinical data for a stratified relapse study or even an upfront window in a very-high-risk population were published for a combination of HDAC and PI3K inhibition in MYC-driven MB²⁰², the use of a cell-cycle checkpoint inhibitor in combination with cytotoxic chemotherapy^{203–205}, the use of various CDK inhibitors with or without cytotoxic agents^{91–93} and targeting LSD1 in the context of GFI1 and/or GFI1B-driven MB²⁰⁶.

For iSHH (largely corresponding to DN and MBEN histology), two clinical trials were recently stopped

prematurely that evaluated an SKK-like chemotherapy-only strategy¹⁹⁶, but without the addition of intraventricular methotrexate, owing to more progression events than expected (NCT00602667 and NCT0217964). One potential explanation for this result could be the existence of two molecular subtypes of iSHH-MB, one of which (iSHH-I) seems to do much worse on this treatment protocol⁶³. If this split also could be recapitulated in the other study and would not be observed in a clinical trial cohort including SKK therapy with intraventricular methotrexate, the consequent next trial design would stratify patients with iSHH into a higher risk subtype that is in need of intraventricular methotrexate to control disease in the entire CNS and a lower-risk subtype that might be cured without intraventricular methotrexate. Such reverse translational approaches to understand the biology of responders versus non-responders are possible only if tumour tissue is obtained from every patient in a clinical trial together with very thorough documentation of imaging, toxicity and clinical data.

For infants with Group 3 MB, who have a very poor prognosis, there is an urgent need to integrate some of

these novel treatment options into the upfront treatment regimens. Complementary or alternative treatment concepts such as chimeric antigen receptor (CAR) T cell approaches, vaccination strategies, lineage targeting and combinations of these with current standard therapies certainly warrant consideration. As an example, a few adoptive immunotherapy approaches are currently under investigation in MB. Reports highlighted potential therapeutic targets such as PRAME²⁰⁷ and HER2 (REF.²⁰⁸). Furthermore, a clinical trial investigating the effects of HER2-specific CAR T cell therapy in patients with MB is currently ongoing (NCT03500991). However, preclinical evaluation of such approaches would be desirable before being considered for clinical trials.

Overall, tailoring MB treatment intensity to disease risk, treatment strategy and disease biology is still in its infancy, and considerable effort is still needed to reduce the burden of long-term toxicity while further increasing cure rates for our patients suffering from this very heterogeneous group of diseases.

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Author contributions

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