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MINI-SYMPOSIUM

Medulloblastoma genomics in the modern molecular era

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Abstract

Medulloblastoma (MB) represents a spectrum of biologically and clinically distinct entities. Initially described histopathologically as a small, round blue cell tumor arising in the cerebellum, MB has emerged as a paradigm for molecular classification in cancer. Recent advances in genomic, transcriptomic and epigenomic profiling of MB have further refined molecular classification and complemented conventional histopathological diagnosis. Herein, we review the main clinical and molecular features of the four consensus subgroups of MB (WNT, SHH, Group 3 and Group 4). We also highlight hereditary predisposition syndromes associated with increased risk of MB. Finally, we explore advances in the classification of the consensus molecular groups while also presenting cutting-edge frontiers in identifying intratumoral heterogeneity and cellular origins of MB.

INTRODUCTION

Medulloblastoma (MB) is the most common malignant pediatric brain tumor (70). Arising from the cerebellum, the median age of diagnosis is approximately 6 years of age. Clinical manifestations of MB, often due to raised intracranial pressure secondary to hydrocephalus, may be non-specific and include headaches, nausea, early morning emesis and poor academic performance. More specific symptoms, such as ataxia, cranial nerve palsies and visual problems, may be attributable to direct mass effect and/or raised intracranial pressure. Diagnostic work-up includes magnetic resonance imaging and cytologic examination of the cerebrospinal fluid. Clinical risk stratification integrates the aforementioned work-up in the Chang staging system (10). Treatment involves neurosurgical resection, irradiation (usually restricted to patients older than 3 years of age) and cytotoxic chemotherapy. The 5-year overall survival of MB hovers around 75%, but many survivors face serious cognitive, endocrine and psychosocial sequalae (29, 43, 72). Outcomes of treatment, as implemented according to conventional clinicopathologic risk stratification, varies according to risk group, with average-risk disease defined in patients older than 3 years with gross total resection and no metastasis at diagnosis (5-year overall survival > 80%) and high-risk disease defined in patients younger than 3 years with subtotal resection at metastasis at diagnosis (5-year overall survival < 70%) (29, 30, 43, 71, 72).

As an embryonal tumor of the cerebellum, MB exhibits an undifferentiated cytology, being composed of small, round uniform cells with hyperchromatic nuclei (94). Such cytology suggests the emergence of these tumors from various stem/progenitor populations during early neurodevelopment. In the histopathologic evaluation of MB, other undifferentiated tumors occurring in the posterior fossa, such as atypical teratoid/rhaboid tumor and the embryonal tumor with multilayered rosettes must be considered in the differential diagnosis (25, 36). Despite early controversy surrounding the classification of MB and other embryonal tumors, such as atypical teratoid/rhabdoid tumor and the now obsolete CNS primitive neuroectodermal tumor (PNET), transcriptomic profiling has definitively separated MB from other intracranial embryonal tumors (45, 81, 94, 103). Additionally, these and other early studies (discussed below) paved the way for a molecular classification of MB that stratifies patients more robustly than clinical parameters alone (81). The consensus molecular subgroups of MB (WNT, SHH, Group 3 and Group 4) were incorporated into the 2016 WHO update on CNS tumor classification (58).

HISTORY

Termed by neurosurgeons Cushing and Bailey in 1925, "medulloblastoma" was initially described as a cerebellar tumor in children (2). The embryonal derivation of MB was reflected in its nomenclature despite no "medulloblast" ever being definitively identified (78). Nonetheless, defining clinical characteristics, including a cerebellar localization, metastatic tendency and male preponderance, were appreciated in early descriptions (16). Furthermore, the extent of neurosurgical resection was identified as a key determinant of survival, as patients undergoing biopsy alone

fared poorly compared to those undergoing more complete resection (2).

Though roentgen therapy was used to treat MB post-operatively in Cushing's era, outcomes did not improve significantly until almost 1950, when craniospinal irradiation (CSI) of the entire neuraxis emerged (76). The importance of such therapy highlights previous observations that MB could spread along the leptomeninges, seed the cerebrospinal fluid with abnormal cells, and recur in distant sites along the neuraxis (42). Despite favorable survival outcomes, exposure of younger patients to CSI often led to neurocognitive and neuroendocrine deficits (38, 52). Furthermore, the risk of secondary malignancies, particularly high-grade gliomas, also increased as a result of CSI (12).

The efficacy of adjuvant chemotherapy in treating MB was initially demonstrated in the late 1970s. These early studies utilized vincristine and lomustine after surgery and radiotherapy. Despite some limitations, these early studies strongly suggested a survival benefit conferred by chemotherapy for patients with more extensive disease at diagnosis (105). Subsequent addition of platinum-based agents formed the backbone of the modern chemotherapeutic regimens used today (73, 74). Given the adverse sequelae associated with CSI, risk stratification for multimodal management hinged, until the molecular era, on age, extent of resection and presence or absence of metastasis.

MOLECULAR SUBGROUPS OF MB: OVERVIEW

MB represents a biologically and clinically heterogenous disease that can vary widely with respect to demographic biases, phenotypic presentation and clinical outcomes. Resolving the varied clinical behavior of some tumors by molecular biomarkers has long represented a key hurdle in dissecting the intertumoral heterogeneity within MB. For instance, nuclear β-catenin expression in the tumors of patients with favorable outcome foreshadowed the eventual identification of the concordant WNT group of MB(26, 29). Similarly, histopathologic correlates of patient outcome were also identified. For example, desmoplastic morphology and a relatively favorable prognosis in pediatric MB patients recapitulates a subset of SHH group tumors, while a large cell/anaplastic (LCA) morphology is associated with poor prognosis and *MYC* amplification, eventually being codified into Group 3 tumors (1, 3, 31, 39, 64, 79, 81). Such diversity in clinical behavior and molecular phenotype strongly motivated the consideration of MB as a composite of distinct entities.

Early transcriptomic studies by microarrays identified between four and six transcriptomic groups of clinical relevance, dependent on cohort size and clustering approaches (11, 50, 65, 108). From these efforts, the four consensus molecular groups (WNT, SHH, Group 3 and Group 4) emerged (107). These molecular groups have distinct demographic features, genetic lesions and gene expression patterns, forming a new framework for studying the disease in the laboratory and the clinic. Additionally, these molecular groups exhibit drastically divergent responses to conventional therapy, enabling molecularly guided risk stratification with the potential to abrogate some of the treatment-related sequelae that impact quality of life in survivors.

With the emergence of high-density DNA methylation arrays to query the epigenomes of many MBs, additional heterogeneity and subtypes have been defined within molecular subgroups (8, 63, 98) (Figure 1A). Though consensus on the definition, nomenclature and methodology required to define these subtypes is ongoing, such additional granularity will likely aid detailed exploration of MB tumor biology while informing clinical assessment. Furthermore, such heterogeneity among epigenetically defined subtypes highlights a potential avenue into understanding chromatin and epigenetic dysregulation as common themes in MB biology (Figure 1B).

WNT-activated MBs

Though only accounting for approximately 10% of MB diagnoses, WNT-activated MBs carry the best prognosis with over 95% of children surviving this disease after 5 years (8, 29, 108). Tumors usually occur in older children (>4 years) with equal incidence between males and females (107). These tumors are also rarely metastatic at diagnosis (Figure 2A). Of note, adults with WNT tumors tend not to have the favorable outcome seen in childhood disease (13, 89).

Readily identifiable by a WNT gene expression signature, these tumors are so named due to activation of the canonical Wingless (WNT) signal transduction pathway (14, 26, 117). Nearly 90% of WNT MBs harbor somatic activating mutations in exon 3 of *CTTNB1* (63). These mutations stabilize the gene product,

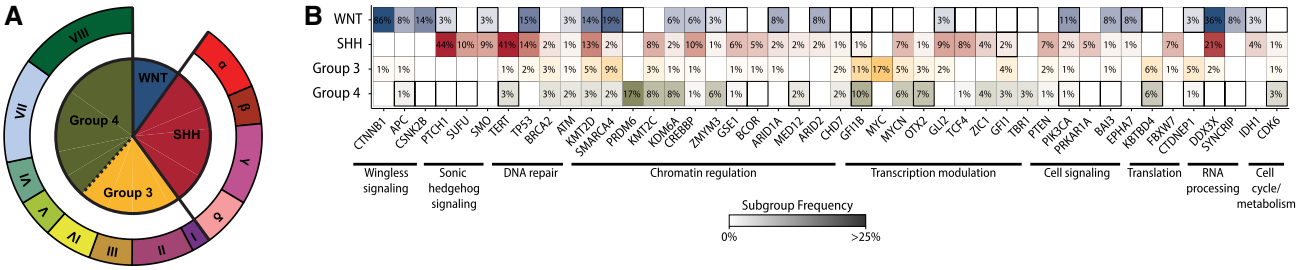

Figure 1. *Molecular classification of medulloblastoma.* **A**. Consensus molecular groups of MB are depicted according to relative frequency of incidence while emerging molecular subtypes of SHH (α, β, γ, δ) and Groups 3/4 (I–VIII) tumors are shown on the outer ring. **B**. Mutational landscape of the molecular groups of medulloblastoma is shown in a heatmap with genes arranged according to functional classes.

β-catenin, preventing its degradation by a cytoplasmic destruction complex (containing APC) and facilitating its unfettered translocation to the nucleus to act as a transcriptional co-activator of TCF/LEF family transcription factors (24, 37). Most patients whose tumors lack somatic *CTTNB1* mutations carry pathogenic germline *APC* variants, necessitating genetic testing for Turcot syndrome in these patients (113). Therefore, constitutive activation of the WNT pathway leading to cellular growth and proliferation in these tumors may emerge as a result of increased stability of β-catenin itself or hampered degradation.

Additional recurrently mutated genes in WNT tumors include *DDX3X*, *SMARCA4*, *TP53*, *CSNK2B*, *PIK3CA* and *EPHA7* (63). While *SMARCA4*, *PIK3CA* and *TP53* are commonly mutated across a variety of human cancers, mutations in *CSNK2B* highlight the essential role of WNT signaling in these tumors as it encodes the β-subunit of casein kinase II, a positive regulator of WNT signaling (21, 46, 61, 84, 115). *DDX3X* encodes an RNA helicase that may promote WNT tumorigenesis by expanding the population of lower rhombic lip progenitors, the putative cell of origin for these tumors (32, 92). *EPHA7* also plays a critical role in developmental patterning of neuronal populations, yet the exact molecular pathogenesis underlying such mutations remains unknown (17, 82). Given the implication of chromatin dysregulation across molecular subgroups of MB, mutations in *SMARCA4* and other members of the SWI-SNF chromatin remodeling complexes in WNT tumors underscores subgroup-specific dependencies and cellular vulnerabilities underlying tumorigenesis.

The genomes of WNT MBs tend to be cytogenetically balanced, with the exception of monosomy 6 occurring in up to 85% of tumors (67). Despite the high frequency of hallmark genetic events in WNT tumors, utilizing only monosomy 6 and *CTTNB1* mutations as WNT tumor biomarkers will fail to identify up to 15% of WNT MBs. WNT subgroup heterogeneity manifests in two age-related subtypes, stratifying children and adults.(8) Of note, the frequency of chromosome 6 euploidy is much higher in adults. As outcomes are generally favorable for children with WNT MBs, current efforts in this patient population are geared toward therapy de-escalation and minimizing toxicities (51).

SHH-activated MBs

SHH-activated MBs account for approximately two-thirds of MBs in infants (<3 years) and adults (>16 years), while

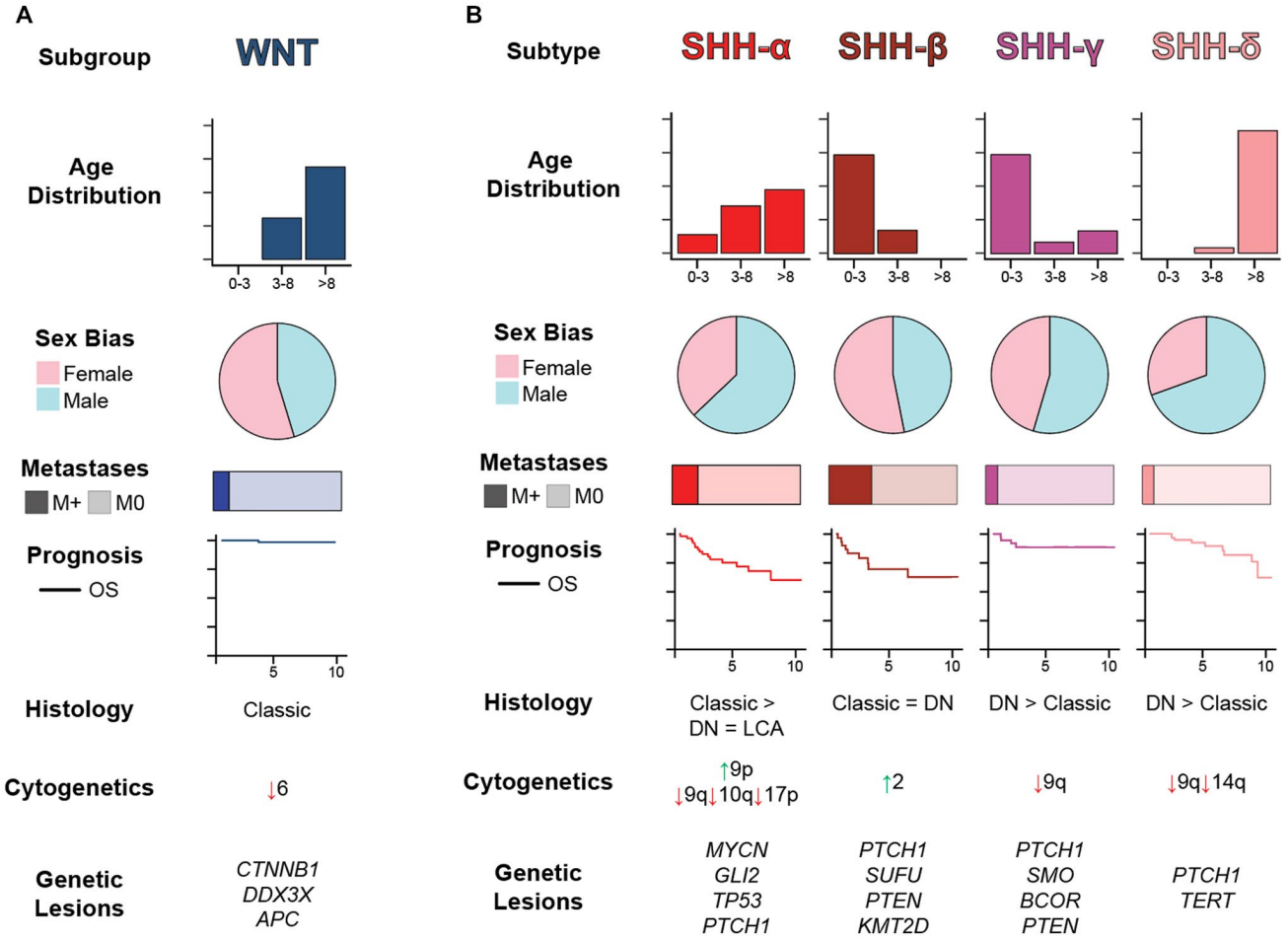

Figure 2. *Summary of WNT and SHH medulloblastomas.* A. WNT MBs are summarized by key clinicodemographic and molecular features. B. SHH MBs are summarized according to molecular subtypes proposed by Cavalli et al.

only accounting for around 15% of MBs in children (ages 3–16) (49). Unlike the largely homogeneous WNT MBs, SHH MBs exhibit a striking degree of biological, pathological, and clinical heterogeneity (8, 98) (Figure 2B). The prognosis of these tumors is largely dictated by genetic factors in addition to clinicopathologic parameters such as patient age, metastatic status and morphology (101).

Named for activation of the sonic hedgehog (SHH) signaling pathway, SHH MBs possess alterations in genes leading to ligand-independent activation of this canonical signaling pathway, facilitating uncontrolled cellular growth and proliferation (18, 33, 111). Such alterations include loss-of-function mutations or deletions in *PTCH1* and *SUFU*, activating mutations of *SMO* and amplifications of *GLI1*, *GLI2* and/or *MYCN* (63). In canonical SHH signaling, soluble SHH ligand binds to PTCH1 on the cell surface, thereby de-repressing SMO. Activated SMO can then transduce the SHH signal intracellularly by releasing SUFU-mediated repression of GLI1/2, allowing these transcription factors to translocate to the nucleus and to elicit expression of target genes, such as *MYC* family proto-oncogenes, growth-promoting cyclins and *PTCH1* itself (to effect pathway feedback inhibition) (23, 69). A molecular understanding of SHH MBs has facilitated the implementation of molecularly targeted therapies with SMO inhibitors in skeletally mature patients (48, 90, 91).

The hallmark cytogenetic events in SHH MBs include losses of chromosomes 9q and 10q, potentiating loss of heterozygosity for *PTCH1* (located on 9q) and *SUFU* (located on 10q) (48, 63, 101, 107). Haploinsufficiency of these crucial negative regulators of SHH signaling underscores the role of *PTCH1* and *SUFU* as tumor suppressors (106). Additionally, loss of function mutations, either germline or somatic/mosaic, in *TP53* can lead to defects in DNA repair and may contribute to clustered chromosomal rearrangements, known as chromothripsis, which are observed in tumors with coincident oncogene amplifications (88). *TP53* mutations in children and adolescents with SHH MBs portend an abysmal prognosis, in stark contrast to the prognosis for WNT tumors with somatic *TP53* mutations (116). As such, the SHH MB with *TP53* mutation is listed separately in the WHO classification and is considered very high risk clinically (58). Such age-dependent segregation of genetic lesions is also highlighted by the predominance of somatic *TERT* promoter mutations in nearly all adults with SHH MBs while only 10%–20% of tumors in pediatric patients harbor such events (48). In addition to WNT tumors, *DDX3X* is also mutated in SHH MBs, albeit at a slightly lower frequency of about 20% (63).

Other genes recurrently altered in SHH tumors include classes of chromatin modifiers, transcriptional regulators and signal transduction components. *KMT2C* and *KMT2D*, mutated in 7% and 13% of SHH MBs, respectively, are members of the MLL/COMPASS family and methylate H3K4 to regulate promoters and/or enhancers (83). Hotspot mutations in *IDH1*, occurring in 4% of SHH MBs, mirror the hypermethylation phenotype observed in adult gliomas (9, 63, 68). Mutations in *PTEN*, a negative regulator of the pro-proliferative PI3K/AKT pathway, occur in 7% of SHH MBs and may also confer intrinsic or acquired resistance to molecular therapies against SHH pathway activation (60). Despite poorly understood molecular mechanisms of the underlying epigenetic or signaling cascade vulnerability, constitutive activation of SHH likely synergizes with dysregulation of chromatin and canonical signal transduction pathways to promote tumorigenesis in vulnerable cell populations (55, 97, 100).

Intertumoral heterogeneity among SHH MBs has been substantiated at both clinical and molecular levels (8, 98). Four distinct subtypes, termed α, β, γ and δ, with various demographic compositions and molecular landscapes have been identified (8). Among patients younger than 5 years, two comparable subtypes, iSHH-I/II (corresponding to SHH-β/γ), have been identified with 5-year progression-free survivals of approximately 25% and 75%, respectively (93). Additionally, comparison of single-cell RNA sequencing of SHH MBs and cerebellar developmental atlases has identified age-related developmental trajectories that seem to recapitulate varying degrees of neuronal differentiation between SHH tumors in infants and older children (40). Taken together, these new SHH MB data highlight advances in linking tumor biology to clinical behavior.

GROUP 3 MBS

Occurring commonly during infancy and early childhood, Group 3 tumors comprise approximately a quarter of MBs. These tumors are also twice as common in males and are noted for a high incidence of metastasis at the time of presentation (107). Considered the most aggressive MB subgroup, Group 3 tumors confer a 5-year overall survival of <60% (11, 65). Certain hallmark genomic features, such as *MYC* amplification, represent extremely high-risk disease (63, 79, 80). Aneuploidy, particularly isochromosome 17q, gains of chromosomes 1q and 7 and losses of chromosome 8, 10q and 16q, is notable among Group 3 tumors (67). The naming of Group 3 tumors highlights the current lack of framework for unifying molecular derangements to underlying tumor biology in this molecular subgroup.

Nearly 20% of Group 3 tumors are characterized by high-level *MYC* amplification (63, 67). Aberrant activation of MYC functions as a central node in a myriad of pro-tumorigenic cellular pathways, including mRNA processing and protein translation (19). Additional gene level amplifications include *MYCN* (5%) and *OTX2* (3%). The contribution of *MYCN* to underlying MB tumor biology is well appreciated with roles in tumor initiation, maintenance and progression (47, 77). As a master transcriptional regulator in neurodevelopment, OTX2 is thought to confer a stem-like state to MB cells (4, 5). Additionally, MYC and OTX2 may function synergistically to promote Group 3 tumorigenesis through transcriptional cross-regulation (6).

In addition to overexpression of the aforementioned genes as a result of gene amplification and other genetic events, *GFI1* and *GFI1B* are upregulated in ~ 15% of Group 3 MBs, in a mutually exclusive manner (63). These transcriptional repressors are key dictators of developmental cell fate decisions (22, 53). The mechanism governing overexpression of these genes occurs through enhancer hijacking, whereby

structural variants juxtapose normally distant and often unrelated gene regulatory elements with the promoters of oncogenes (Figure 3). In Group 3 MBs, highly active enhancers overlapping *DDX31* are repositioned proximal to *GFI1B*, leading to its overexpression (66). Such striking genetic–epigenetic interplay highlights the necessity to contextualize genomic events with annotations of gene regulatory elements.

The landscape of somatically altered genes in Group 3 MBs is relatively sparse with only *SMARCA4*, *KBTBD4*, *CTDNEP1* and *KMT2D* recurrently mutated in greater than 5% of tumors (44, 63, 83). KBTBD4 is a poorly characterized member of the Kelch–BTB–BACK family, which consists of proteins involved in the ubiquitin–proteasome pathway (7). Somatic in-frame insertions in *KBTBD4* are clustered in the conserved Kelch domain, potentially leading to dysregulation of substrate recognition (63). CTDNEP1 functions as a protein phosphatase, with substrates including BMP receptors (95, 96). The molecular pathogenesis of *CTDNEP1* mutations, which can occur as hotspot frameshifts in the phosphatase domain, are poorly understood (44). Whether the contribution of *SMARCA4* and *KMT2D* mutations in Group 3 tumors is distinct from that seen in WNT and SHH MBs, respectively, remains unknown.

GROUP 4 MBS

As the most common molecular subgroup of MB, Group 4 tumors account for up to 40% of all cases and tend to occur in older children (107). Group 4 tumors have a gender bias toward males of nearly 3:1. Despite being considered intermediate in terms of survival, approximately 33% of patients have metastatic disease at presentation, and relapse latency is longer for Group 4 tumors compared to other MBs (8, 86). Like their Group 3 counterparts, Group 4 tumors remain poorly characterized in terms of underlying tumor biology.

Though Group 4 MBs fail to disclose driver genes recurrently mutated at frequencies above 10%, the class of somatically altered genes highlight the likely role of chromatin modifier dysregulation in the molecular pathogenesis of this molecular subgroup (63, 75). Mutually exclusive loss of function mutations in the chromatin modifiers *KDM6A*, *ZMYM3* and *KMT2C* suggest possible convergent dysregulation of the epigenome in tumorigenesis (41, 63, 92). KDM6A functions as a demethylase of H3K27 and associates with the MLL complexes to effect changes in H3K4 methylation (112). KMT2C, a member of the MLL family and COMPASS complex member, can modulate

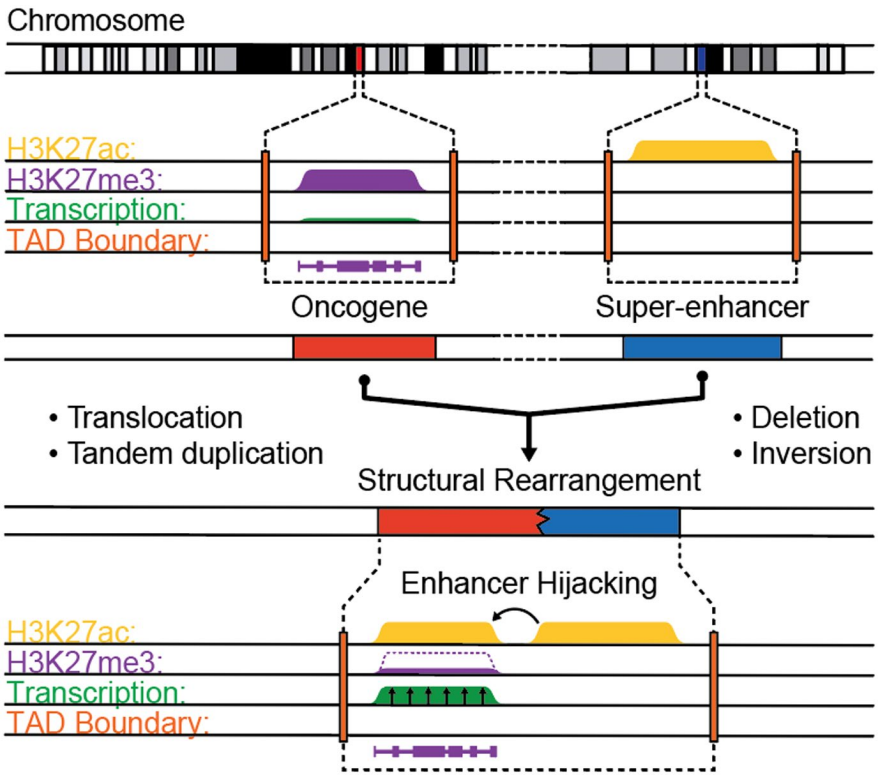

Figure 3. *Schematic mechanism of enhancer hijacking in medulloblastoma.* Juxtaposition of transcriptionally repressed oncogene locus with active gene regulatory elements (eg, super-enhancers) can occur by various structural rearrangements. Such alterations to genomic architecture lead to reorganization of topologically associated domains (TADs, depicted by dashed boxes) by disruption of native boundary elements (orange). As a result, active gene regulatory elements (marked by H3K27ac, yellow) can spread to the normally repressed proto-oncogene promoters (marked by H3K27me3, purple), leading to oncogene transcription (green).

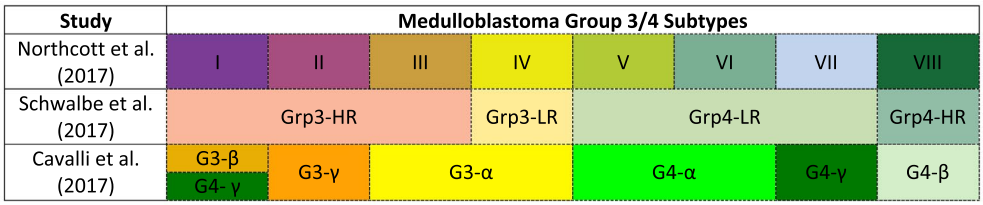

Figure 4. *Overview of proposed Group 3/4 MB subtypes.* Three independent studies have described four to eight molecular subtypes of Group 3 and Group 4 medulloblastoma. While concordance between subtypes across different studies is not definitive, an overlay of these subtypes according to study are depicted above according to nomenclature adopted within each study. LR = low-risk; HR = high-risk.

activity of gene regulatory elements through its H3K4 methyltransferase action at promoters and enhancers (87). ZMYM3 has been described in association other chromatin modifiers and implicated in the DNA damage response (54). Disruptions of these well-described chromatin modifiers may perturb the chromatin and transcriptional regulatory landscape at key developmental gene promoters and/or enhancers to promote Group 4 tumorigenesis. Additionally, disruption of these chromatin modifiers may alter cellular responses to DNA damage.

The most prevalent putative driver event in Group 4 MBs involves the overexpression of *PRDM6* via enhancer hijacking, in which tandem duplications and other structural variants at the *SNCAIP* locus juxtapose a highly active super-enhancer with promoter elements of *PRDM6* (63). PRDM6 has been described as a chromatin modifier and transcriptional regulator in the developing cardiovascular system, though functional validation of its role in MB is lacking (20, 114). *CDK6*, also amplified exclusively in Group 4 tumors, encodes a key cell cycle regulator of the G1-S transition (59, 85). Hotspot mutations in the T-box domain of *TBR1*, a neurodevelopmental transcriptional factor, occur exclusively in Group 4 tumors (28, 44).

Similar to their Group 3 counterparts, Group 4 MBs harbor gene-level amplifications of *MYCN* as well as somatic mutations in *KBTBD4* (63). As amplifications of *OTX2* also occur in Group 4 tumors, the overlapping spectrum of altered genes between Group 3 and Group 4 MBs suggests a possible continuum in terms of tumor biology. At the cytogenetic level, Group 4 tumors are characterized by high rates of isochromosome 17q, losses of chromosomes 8 and 11 and gains of chromosomes 7 (63, 67). Certain cytogenetic events, namely chromosome 11 loss and chromosome 17 gain, have been associated with favorable prognosis in Group 4 MB patients (101).

MOLECULAR SUBTYPES IN GROUP 3/4 MBS

Representing nearly two-thirds of all MBs, Group 3 and Group 4 tumors exhibit a spectrum of clinical behaviors with many patients relapsing despite having average-risk disease (34). Furthermore, molecular heterogeneity within Group 3 and Group 4 MBs has been recognized, with identification of varying numbers of Group 3/4 subtypes using different methods (8, 11, 50, 63, 67, 98). However, the extent to which these clinical and molecular subtypes can ultimately be reconciled remains in question (Figure 4).

Because of differing analytical approaches and cohort composition biases in prior studies, distinct numbers of Group 3/4 subtypes were identified. Northcott et al. utilized t-distributed stochastic neighbor embedding dimensionality reduction and density-based clustering on a cohort of 740 Group 3/4 tumors profiled by DNA methylation array (63). Schwalbe et al. also utilized DNA methylation arrays but implemented non-negative matrix factorization on 243 Group 3/4 tumors (98). Cavalli et al. integrated gene expression and DNA methylation arrays using similarity network fusion on 470 Group 3/4 samples (8). An overview of the molecular subtypes identified in these studies is presented in Figure 4. In attempting to unify these large-scale analyses, Sharma et al. recently performed a meta-analysis based on the aforementioned studies to summarize the second-generation subtypeing of Group 3/4 MBs and developed a random forest classifier for eight molecular subtypes of Group 3/4 MBs based on DNA methylation array (99) (Figure 5).

GERMLINE PREDISPOSITIONS

MB can be associated with rare, hereditary tumor predisposition syndromes. Gorlin syndrome, characterized by damaging mutations in *SUFU or PTCH1*, has been associated with increased risk of MB .(102). Other syndromes associated with aberrant SHH signaling, such as Curry–Jones syndrome (mosaic *SMO* mutations) or Greig cephalopolysyndactyly syndrome (*GLI3* mutations), underscores the dysregulation of SHH pathway as a unifying pathophysiologic mechanism for SHH-activated MB (27, 35, 109). Familial adenomatous polyposis (Turcot) syndrome, characterized by mutations in *APC*, predisposes to WNT MB (15). In addition to developmental signaling axes, other molecular processes commonly affected in germline predisposition syndromes with increased risk of MB include germline defects in DNA damage response/repair machinery, such is in Li–Fraumeni syndrome (*TP53* mutations) and constitutional mismatch repair (mutations in *MLH1*, *MSH2*, *MSH6* or *PMS2*) (48, 56, 57, 62, 88, 104).

Recent studies have identified damaging germline mutations in approximately 10% of all patients with MB (113). The most commonly altered predisposition genes include *APC*, *BRCA2*, *PALB2*, *PTCH1*, *SUFU* and *TP53*, accounting for 6% of MBs. Of note, the burden and distribution of germline predisposition to MB is not distributed uniformly across

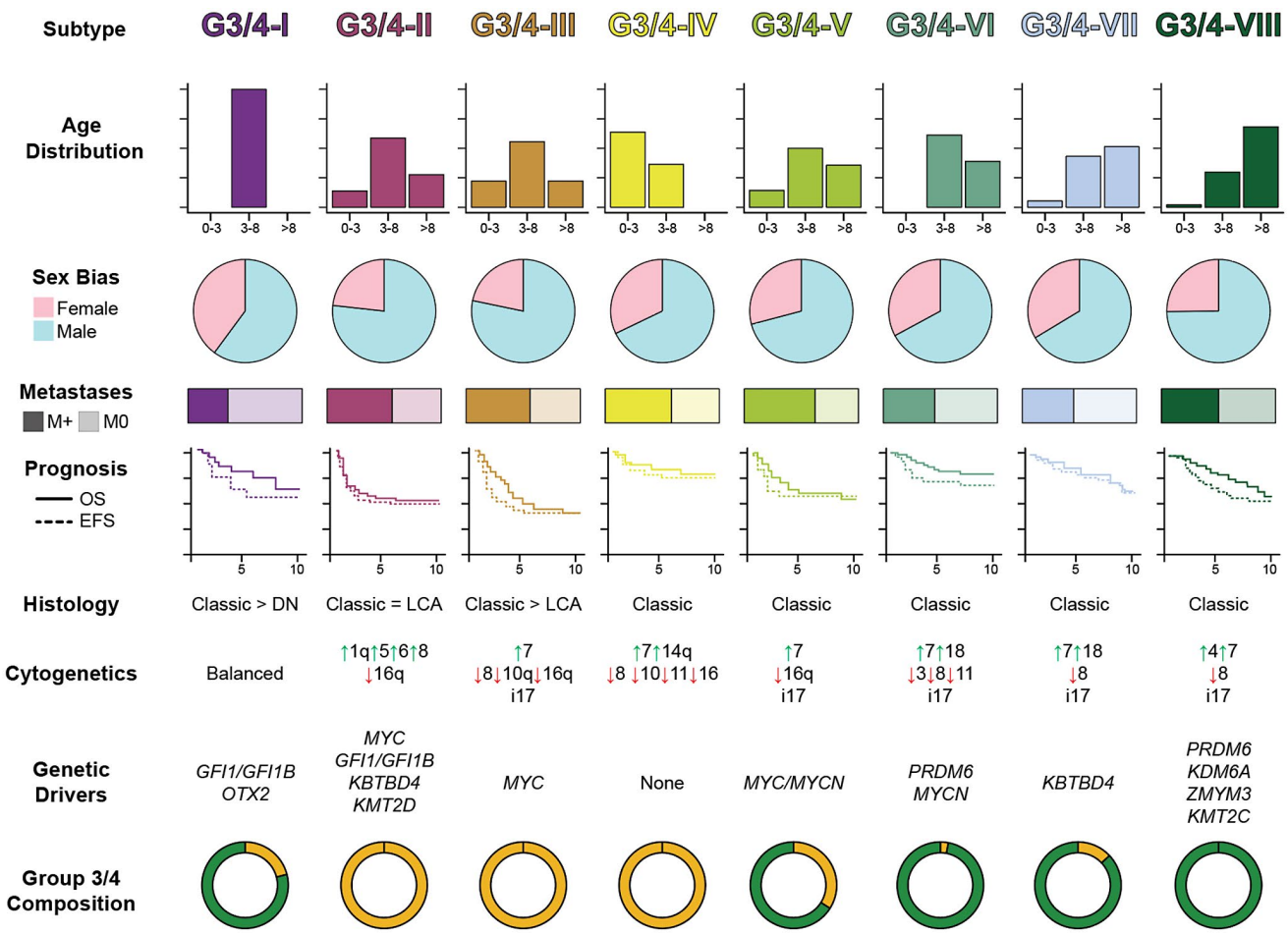

Figure 5. *Summary of Group 3/4 medulloblastoma subtypes.* Clinicopathologic and molecular summary of eight molecular subtypes of Group 3 and Group 4 medulloblastomas according to Northcott et al. (2017) and Sharma et al. (2019). The composition of each subtype according to consensus Group 3 or Group 4 profiling is shown at the bottom of the panel. LCA = large cell anaplastic; DN = desmoplastic/nodular.

molecular groups. While 20% of patients with SHH MBs harbor predisposing germline variants, such predisposition based on known hereditary tumor genes is much rarer in Group 3 and Group 4 tumors. Furthermore, the specific mutations associated with germline predisposition dictate risk for MB and thereby influence the age at diagnosis as well as association with molecular group. Clinical manifestations and syndromic symptomatology vary according to specific genetic predisposition (Figure 6). Coupled with the incidence of cancers in the family history, the various altered predisposition genes in MB underscore the differing necessities for genetic testing, family counseling and surveillance monitoring.

OUTLOOK

The modern era of MB genomics has afforded tremendous insights into basic tumor biology, refined molecular diagnostic approaches and informed clinical management. Nonetheless, considerable effort is needed to tailor treatment strategies to risk stratification guided by conventional histopathologic and clinical features and adapted to the context of MB molecular subgroups and subtypes. Furthermore, molecular risk features identified through large-scale genomics of retrospective trials must be validated and contextualized in prospective studies. Implementation of molecularly guided therapies requires not only careful consideration of rational drug targets based on tumor biology but also the rigorous evaluation of these agents in appropriate preclinical models. Furthermore, tumor evolution and the nature of relapsed disease must be explored comprehensively to guide efforts to salvage patients who fail first-line therapies. Likewise, systematic characterization of patient germlines must be conducted beyond known cancer predisposition genes to uncover previously unknown genetic risks that will guide long-term surveillance and genetic counseling. Finally, despite incremental advances in survival for certain patients, improvements in overall survival must also be considered in terms of quality of life with effort geared toward therapeutic de-escalation in patients with favorable outcome.

While appreciation of intertumoral heterogeneity among MBs has facilitated biologically and clinically relevant

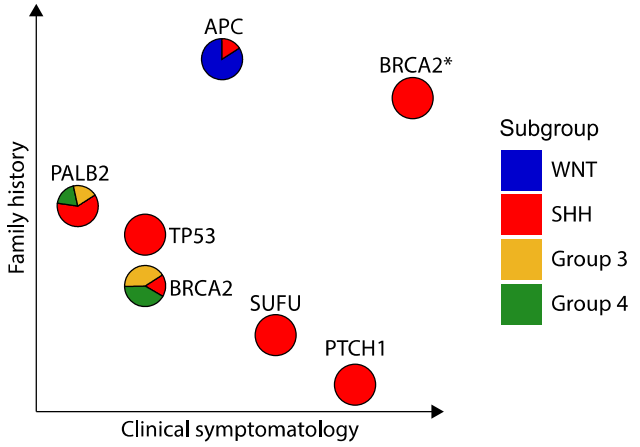

Figure 6. *Germline predisposition genes in medulloblastoma.* Six most commonly mutated genes (BRCA2* = compound heterozygous mutations) predisposing to medulloblastoma are depicted. Molecular subgroups of tumors associated with alterations in respective germline predisposition genes are plotted as pie charts. Distance along each axis represents the proportion of patients with positive family history or recognizable clinical signs of germline predisposition syndromes.

molecular classification, deeper characterization of these tumors using single-cell sequencing techniques has uncovered additional layers of intratumoral heterogeneity. Furthermore, such approaches can be utilized to unravel normal developmental cascades of cellular differentiation to correlate the transcriptomic signatures of individual tumor cells to specific cellular populations within the developing cerebellum. Two recent single-cell transcriptomic studies have leveraged the developing mouse cerebellum as a reference atlas for uncovering cellular hierarchies and transcriptional programs underlying the various molecular subgroups of MB (40, 110). In addition to recapitulating granule neuron progenitors as the cellular origins for SHH MBs, both subgroups identified unipolar brush cells are the putative cellular origins of Group 4 MBs. Additionally, age-associated developmental hierarchies were uncovered for SHH MBs, wherein the differentiation state of cells within a tumor was inversely correlated with age of the patient at diagnosis. Furthermore, the cellular compositions of Group 3/4 MBs was shown to vary according to proportion of differentiated vs. undifferentiated cells, with Group 3 tumors largely comprised of the latter. These novel insights may suggest the necessity to reconsider Group 3/4 MBs as a continuum, particularly for those subtypes intermediate between Group 3 and Group 4.

While these studies implicate specific cellular and mechanistic susceptibilities to MB tumorigenesis in the context of normal cerebellar development, additional characterization of MB at the epigenomic and chromatin level will be necessary to deconvolute the respective contributions of cellular origins and transcriptional aberrancies imposed by mutations in epigenetic machinery to the overall signature of a given tumor. With the emergence of single-cell approaches to profile the chromatin landscape and transcriptional factor binding, refinement of the molecular structure of MB will hopefully continue to motivate a more profound understanding of this devastating disease.

CONCLUSIONS

The modern molecular era of MB genomics has facilitated the classification of the disease into WNT, SHH, Group 3 and Group 4 tumors. These molecular subgroups recapitulate distinct tumor biology as evidenced by demographic biases, distinct genetic lesions and clinical behavior. Further subtyping of the MBs has unveiled additional granularity in SHH and Group 3/4 tumors. While continued efforts are required to reconcile the various proposed MB subtypes, such information will provide a molecular framework for the design of rational and targeted clinical trials in attempts to improve survival for high-risk patients while mitigating long-term sequelae in lower risk patients by de-escalation of therapy. Continued exploration of tumor biology underlying MB will afford crucial insights into novel oncogenic mechanisms and uncover additional therapeutic vulnerabilities. As such, MB represents a paradigm of integrated clinicomolecular study of pediatric cancers.

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