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## Subgroup and subtype-specific outcomes in adult medulloblastoma

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## Abstract

Medulloblastoma, a common pediatric malignant central nervous system tumour, represent a small proportion of brain tumours in adults. Previously it has been shown that in adults, Sonic Hedgehog (SHH)-activated tumours predominate, with Wingless-type (WNT) and Group 4 being less common, but molecular risk stratification remains a challenge. We performed an integrated analysis consisting of genome-wide methylation profiling, copy number profiling, somatic nucleotide variants and correlation of clinical variables across a cohort of 191 adult medulloblastoma cases identified through the Medulloblastoma Advanced Genomics International Consortium. We identified 30 WNT, 112 SHH, 6 Group 3, and 41 Group 4 tumours. Patients with SHH tumours were significantly older at diagnosis compared to other subgroups ( $p < 0.0001$ ). Five-year progression-free survival (PFS) for WNT, SHH, Group 3, and Group 4 tumours was 64.4 (48.0–86.5), 61.9% (51.6–74.2), 80.0% (95% CI 51.6–100.0), and 44.9% (95% CI 28.6–70.7), respectively ( $p = 0.06$ ). None of the clinical variables (age, sex, metastatic status, extent of resection, chemotherapy, radiotherapy) were associated with subgroup-specific PFS. Survival among patients with SHH tumours was significantly worse for cases with chromosome 3p loss (HR 2.9, 95% CI 1.1–7.6;  $p = 0.02$ ), chromosome 10q loss (HR 4.6, 95% CI 2.3–9.4;  $p < 0.0001$ ), chromosome 17p loss (HR 2.3, 95% CI 1.1–4.8;  $p = 0.02$ ), and *PTCH1* mutations (HR 2.6, 95% CI 1.1–6.2;  $p = 0.04$ ). The prognostic significance of 3p loss and 10q loss persisted in multivariable regression models. For Group 4 tumours, chromosome 8 loss was strongly associated with improved survival, which was validated in a non-overlapping cohort (combined cohort HR 0.2, 95% CI 0.1–0.7;  $p = 0.007$ ). Unlike in pediatric medulloblastoma, whole chromosome 11 loss in Group 4 and chromosome 14q loss in SHH was not associated with improved survival, where *MYCN*, *GLI2* and *MYC* amplification were rare. In sum, we report unique subgroup-specific cytogenetic features of adult medulloblastoma, which are distinct from those in younger patients, and correlate with survival disparities. Our findings suggest that

clinical trials that incorporate new strategies tailored to high-risk adult medulloblastoma patients are urgently needed.

## Keywords

Adult; Medulloblastoma; DNA methylation profiling; Molecular groups; Risk stratification

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## Introduction

Medulloblastoma is among the most common malignant brain tumours of childhood with an incidence of 0.48 per 100,000; however, in adults, these tumours are less common with an incidence of 0.15 per 100,000 [23, 26, 28]. Due to low patient numbers and a lack of robust clinical trials, treatment standards of care for adult medulloblastoma patients have not been established [8, 9, 21]. Current approaches include maximum safe resection followed by craniospinal irradiation, with or without adjuvant chemotherapy. However, because adults over the age of 21 have been historically excluded from pediatric cooperative group studies, there is a paucity of risk stratification schemes which could guide treatment [20]. For this reason, many adult patients are usually treated with surgery and standard dose craniospinal irradiation only.

Whereas all medulloblastoma are categorized molecularly into four distinct subgroups, Wingless-type (WNT), Sonic Hedgehog (SHH), Group 3 and Group 4, adult medulloblastoma is considered to be a distinct entity from their pediatric counterparts [20]. In adults, the majority of medulloblastoma fall into the SHH subgroup (60%) followed by Group 4 and WNT tumours; Group 3 tumours are rare [11, 15, 16, 29, 37, 38]. Within subgroups, subtype-specific transcriptional and epigenetic signatures have been identified, leading to further identification of risk groups [6, 24, 27]. Such examples include *TP53* mutations in SHH, *MYC* amplifications and isochromosome 17q in Group 3, and isochromosome 17q, *MYCN* amplifications, and loss of 11q in Group 4 [27]. Unlike those arising in children, adults with WNT tumours are postulated to have a worse prognosis, but this may be therapy-dependent [22]. In adults, the majority of SHH tumours fall into the SHH /SHH-4 group, have an enrichment for *TERT* promoter mutations, highly recurrent U1 mutations, a paucity of somatic *TP53* mutations, and rare to non-existent germline *TP53* mutations [6, 30, 36]. Recently, it has been suggested in a single cohort that SHH /SHH-4 are comprised of two epigenetic subsets termed aSHH-MBI and aSHH-MBII with prognostic relevance associated with *VEGFA* expression [18]. However, clinical-molecular correlates within medulloblastoma subtypes have rarely been reported, especially within a younger cohort of predominantly older adolescent and young adult tumours [7]. In this study, we outline the landscape of adult medulloblastoma subtypes in a large cohort of molecularly characterized tumours.

## Materials and methods

### Patient cohort

One hundred and ninety-three cases of medulloblastoma in patients over the age of 15 years were identified through the Medulloblastoma Advanced Genomics International Consortium (MAGIC), which had available genome-wide methylation profiles, and classified using the Molecular Neuropathology 2.0 classifier [5]. Survival information was available for 154 cases. Other clinical data collected included age at diagnosis, metastatic status (metastatic versus nonmetastatic), extent of resection [gross total resection (GTR)/near total resection (NTR) versus subtotal resection (STR)], chemotherapy (yes versus none), radiation [craniospinal irradiation (CSI) with boost versus focal/whole brain irradiation versus none], relapse details (local only versus metastatic) (Table 1, online resource). TERT promoter status was determined as previously described [30]. A validation cohort of 25 Adult Group 4 were obtained from the Burdenko Neurosurgical Institute, where 7 were profiled in the main cohort (Table 2, online resource). A pediatric cohort of previously described Group 4 samples with available clinical annotations was included for comparison (Table 3, online resource) [6]. Samples were all collected under approval of the Hospital for Sick Children Research Ethics Board and local institutional research ethics boards.

### Genome wide DNA methylation profiling

Samples were analyzed on the Illumina Infinium HumanMethylation450 or HumanMethylationEPIC array at the Centre for Applied Genomics at the Hospital for Sick Children and the PM-OICR Translational Genomics Laboratory and Princess Margaret Genomics Centre (Toronto, Ontario) according to the manufacturer's instructions. Subgroup and subtype (Group 3 and Group 4) were determined using the Molecular Neuropathology 2.0 classifier version 1.0 (<https://www.molecularneuropathology.org/mnp>) and t-distributed stochastic neighbor embedding (t-SNE) analysis based on signature marker expression as previously described [1, 5, 32]. Subgroup affiliation could not be reliably assigned to four samples. Distance between samples was calculated using Pearson correlation coefficient as the distance measure and the same distance matrix was used to perform the t-SNE analysis using the Rtsne package version 0.11.17. The following non-default parameters were used: theta = 0, is\_distance = T, pca = F, max\_iter = 10,000, perplexity = 30. All analyses were conducted in the R Statistical Environment (v4.0.2). The DNA methylation data sets unique to this study are available at Mendeley Data, <https://doi.org/10.17632/bbtyhpw7s4.1>.

### RNA sequencing

Strand-specific RNA sequencing including identification of exonic somatic nucleotide variants, available in 74 cases, was performed as previously described and available in the European Genome-Phenome Archive (EGA) (EGAD00001006305, EGAD00001004435, EGAD00001001899, and EGAD00001004958) [34].

## Copy number inference from methylation arrays and identification of recurrent broad events

Copy number segmentation was performed from genome wide methylation arrays using the *conumee* package (v0.99.4) in the R statistical environment (v4.0.2) as previously described [12, 35]. Broad copy number events were determined using visual inspection of copy number plots.

## Statistical analysis

Progression-free survival (PFS) was analyzed by the Kaplan–Meier method and *p* values reported using the log-rank test. Associations between covariates and risk groups were tested by the Fisher’s exact test. Univariable and multivariable cox proportional hazard regression was used to estimate hazard ratios including 95% confidence intervals. The proportional-hazards assumption was tested using the *cox.zph* function in the *survival* package and graphical inspection of Schoenfeld residual plots and was not statistically significant for any of the covariates. All statistical analyses were performed in the R statistical environment (v4.0.2), using R packages *survival* (v3.2–7), and *ggplot2* (v3.3.2) and SAS software, Version 9.4 of the SAS System for Unix (SAS Institute Inc., Cary, NC, USA) [31].

## Results

### DNA methylation profiling

Genome-wide methylation profiling was available on 191 adult medulloblastoma samples using either the Illumina HumanMethylation450 or HumanMethylationEPIC arrays and the Heidelberg brain tumour classifier. To discern the extent of heterogeneity within the cohort, we applied unsupervised clustering using the most variably methylated probes with a standard deviation over 0.25. A distance matrix was constructed using 1 minus the weighted Pearson correlation. Both t-SNE analysis and spectral clustering were applied to the resulting distance matrix. We investigated the distribution of 191 samples alongside a large reference cohort of CNS tumours [5]. These tumours formed five distinct DNA methylation classes (WNT, SHH child/adult, SHH-infant, Group 3, Group 4 and two non-classifiable samples) (Fig. 1a, online resource). A more focused t-SNE analysis of DNA methylation patterns of these 191 cases with a medulloblastoma reference cohort confirmed the distinct patterns of the four adult medulloblastoma subgroups (Fig. 1b, online resource). As previously described, we also identify three primary groups of adult medulloblastoma, with SHH being the predominant group followed by Group 4 and WNT (Fig. 1b).

### Demographic and clinical landscape of adult medulloblastoma

Demographics and clinical features of the cohort are summarized in Table 1. Our study included 191 adult medulloblastoma samples, 189 (99.0%) to which a subgroup could be confidently ascribed (Table 1, online resource). We identified 30 WNT (15.8%), 112 SHH (59.3%), 6 Group 3 (3.2%), and 41 Group 4 (21.7%) tumours. The most frequent SHH subtype was SHH /SHH-4 ( $n = 106$ , 94.6%); of these, 51 (48.1%) were aSHH-MBI and 55 (51.9%) were aSHH-MBII [18]. We then proceeded to assign the newly described Group 3/4 subtypes, with the predominant group being subtype VIII/8 ( $n = 24$ , 58.5%) [32]. The

median age of the cohort was 26.7 years (IQR 18.0–32.0) and statistically significant age differences were seen across the subgroups, with SHH medulloblastomas being the oldest at diagnosis (median 27.0 years, IQR 20.9–37.8) ( $p < 0.0001$ ) (Table 1, Fig. 1a, c). The majority were male (61.1%), had non-metastatic disease at diagnosis (80.9%), underwent GTR/NTR (84.3%), and received chemotherapy (81.2%). Radiation details were available for 116 cases. One hundred (86.2%) received CSI with a focal boost, six (5.2%) received focal irradiation alone, one (0.9%) received whole brain irradiation alone, and four (3.5%) did not receive irradiation. An additional five patients were irradiated but details were not available. The dose of CSI was available for 95 cases. Twenty patients received 24 Gray (Gy), 29 received 30–35 Gy, and 46 received 36 Gy. Of the 46 cases with available relapse data, 17 (37.0%) relapsed locally and 29 (63.0%) had metastatic relapses.

### Subgroup and subtype-specific chromosomal aberrations

The overall patterns of broad copy-number changes were similar to previous reports (Figs. 1a, 2) [6, 16, 17]. WNT tumours were enriched for monosomy 6; however, as previously described, this was less common than in the childhood WNT cases (43.3%) [33]. Of the six WNT cases with available *TP53 DNA* sequencing, one (16.7%) mutation was detected. SHH tumours were enriched for 3p loss (8.0%), 3q gain (20.5%), 9q loss (27.7%), 10q loss (13.4%), 14q loss (15.2%), 17p loss (15.2%). *MYCN*, *GLI2* and *PTEN* mutations were infrequent (4.1%, 6.8%, and 2.7%, respectively). *MYCN* and *GLI2* amplifications were also infrequent (3.6% and 1.8%, respectively). Of the 74 cases with available *TP53* sequencing, three (4.1%) were mutated; one case in an SHH $\alpha$ /SHH-3 and the other two in SHH / SHH-4. SHH tumours were enriched for mutations in *CREBBP* (13.5%), *DDX3X* (43.2%), *FBXW7* (17.6%), *GSE1* (12.2%), *LHX1* (10.8%), *PTCH1* (35.1%), *SMO* (23.0%), and *UI snRNA* (93.5%) (Fig. 2) [36]. Within the two molecular adult SHH subtypes [18], there were no significant distribution differences in broad copy-number changes with the exception of 14q loss; in aSHH-MBI, 14q loss was found in 29.4% of cases compared to 3.6% in the aSHH-MBII group ( $p = 0.0003$ ) (Fig. 2, online resource). Among cases with available data, the median *VEGFA* fragments per kilobase per million (FPKM) was 0.78 (IQR 0.54–1.20). *VEGFA* FPKM were equally distributed between the two subtypes; median *VEGFA* FPKM in aSHH-MBI was 0.75 (IQR 0.59–0.95) compared to 0.79 (IQR 0.52–1.58) in aSHH-MBII ( $p = 0.10$ ). Distribution differences in mutational burdens between the two adult molecular SHH subtypes were seen in *FBXW7* (8.8% in aSHH-MBI, 27.8% in aSHH-MBII;  $p = 0.03$ ), *KAT6B* (17.7% in aSHH-MBI, 2.8% in aSHH-MBII;  $p = 0.04$ ), *SMO* (44.1% in aSHH-MBI, 5.6% in aSHH-MBII;  $p = 0.0001$ ), and *XPO1* (17.7% in aSHH-MBI, 2.8% in aSHH-MBII;  $p = 0.04$ ). In Group 3 tumours, there were 2 cases of 1q gain (33.3%), 2 cases of 17p loss (33.3%), 2 cases of 17q gain (33.3%), 1 case of isochromosome 17q (iso17q) (16.7%), and 2 cases of *MYC* amplification (33.3%). Group 4 tumours were enriched for chromosome 8 loss (26.5%), chromosome 11 loss (12.2%), 13q loss (19.5%), iso17q (75.6%). There was a single case of *MYCN* amplification (2.4%) and a single case of *MYCN* gain (2.4%). The distribution of these chromosomal aberrations were similar among the Group 4 subtypes with the exception of chromosome 11 loss (2 cases in V/5, 2 cases in VI/6, 1 case in VIII/8;  $p = 0.0079$ ), and iso17q (3 cases in V/5, 3 cases in VI/6, 3 cases in VII/7, 22 cases in VIII/8;  $p = 0.002$ ).



## Progression-free survival in adult medulloblastoma

Survival across the subgroups and subtypes was determined using a Kaplan–Meier survival analysis. PFS was available for 154 cases and progression events were evenly distributed across the four subgroups. Fourteen of 66 progression events (21.2%) occurred after 5 years. Forty-nine deaths were observed in the cohort, 7 in WNT, 28 in SHH, 2 in Group 3, and 12 in Group 4; deaths were evenly distributed amongst the subgroups ( $p = 0.83$ ). Table 2 outlines the univariate analyses of PFS across the 4 subgroups. Male sex was associated with a trend to worse PFS for Groups 3 and 4 in univariable analysis (HR 0.3, 95% CI 0.1–0.9;  $p = 0.02$ ). For the full cohort, metastatic disease portrayed a trend towards worse PFS (HR 2.1, 95% CI 1.0–4.0;  $p = 0.04$ ) but not within individual subgroups. Neither the receipt of chemotherapy nor subtotal resection were predictive of poor outcome in univariable analysis.

There were no statistically significant survival differences between subgroups ( $p = 0.06$ ) (Fig. 3a). Five-year PFS for WNT, SHH, Group 3, and Group 4 was 64.4 (48.0–86.5), 61.9% (51.6–74.2), 80.0% (95% CI 51.6–100.0), and 44.9% (95% CI 28.6–70.7), respectively. Isochromosome 17q (i17q) predicted poor outcome for the complete cohort but not for the individual subgroups; 5-year PFS for i17q was 49.1% (95% CI 29.5–66.0) compared to 62.6% (95% CI 52.2–71.3;  $p = 0.02$ ) (HR 1.9, 95% CI 1.1–3.2).

Among SHH cases, PFS was significantly worse for cases with 3p loss; 5-year PFS for 3p balanced was 65.2% (95% CI 52.3–75.4) compared to 28.6% (95% CI 4.1–61.2) ( $p = 0.02$ ) (HR 2.9, 95% CI 1.1–7.6) (Fig. 3a, online resource). Survival was significantly worse in 10q loss; 5-year PFS for 10q balanced was 68.0% (95% CI 57.2–81.0) compared to 25.6% (95% CI 9.7–67.7) for 10q loss patients ( $p < 0.0001$ ) (HR 4.6, 95% CI 2.3–9.4) (Fig. 3b). We also observed that among SHH medulloblastoma 17p loss was associated with significantly worse survival: the 5-year PFS for patients with 17p loss was 50.0% (95% CI 22.9–72.2) compared to 63.7% (95% CI 49.8–74.7) for patients with balanced 17p ( $p = 0.02$ ) (HR 2.3, 95% CI 1.1–4.8) (Fig. 3c). Focal deletions of TP53 were not observed and of the 7 tumors with 17p loss and available TP53 mutational status, only one was mutant; with an additional two tumors harboring TP53 mutations without 17p loss. *PTCH1* mutations also was associated with worse survival: 5-year PFS for mutated cases was 51.5% (95% CI 26.8–71.6) compared to 75.2% (95% CI 55.8–87.0) ( $p = 0.03$ ) (HR 2.6, 95% CI 1.1–6.2). Among the cases with *TP53* sequencing data, *TP53* mutation predicted poor outcome (HR 12.6, 95% CI 2.5–64.0;  $p = 0.002$ ). In line with previous data [18], each 1 unit increase in *VEGFA* was associated with worse survival as an increased HR of 1.2 (95% CI 1.0–1.5;  $p = 0.02$ ) (Table 2). For SHH tumours, neither aSHH subtype, 3q gain, 9q loss, nor 14q loss were predictive of PFS (Fig. 3b–e, online resource).

Among SHH cases, a multivariable analysis was undertaken incorporating age, metastatic status, extent of resection, 3p loss, 10q loss, 14q loss, 17p loss. The prognostic value of 3p loss (HR 3.4, 95% CI 1.1–11.0;  $p = 0.04$ ) and 10q loss (HR 5.0, 95% CI 1.9–13.2;  $p = 0.001$ ) remained significant (Table 3).

For Group 4 tumours, chromosome 8 loss was associated with improved survival, where 5-year PFS for chromosome 8 loss was 70.0% (95% CI 22.5–91.8) compared to 34.6%

(95% CI 10.9–60.3) for balanced ( $p = 0.04$ ) (Online resource). This finding was validated in an independent cohort of 25 patients, where 5-year PFS for chromosome 8 loss was 85.7% (95% CI 33.4–97.9) compared to 38.1% (95% CI 9.7–67.1) for balanced ( $p = 0.04$ ) (Online resource; Table 2, online resource). For the combined cohort of 59 Group 4 cases, the 5-year PFS for chromosome 8 loss was 78.4% (95% CI 46.4–92.6) compared to 36.0% (95% CI 16.5–56.0) for balanced ( $p = 0.003$ ) (Fig. 3d). Among the 24 patients with subtyping data available, chromosome 8 loss was not associated with improved survival among subtype VIII tumours (HR 0.5, 95% CI 0.2–1.8;  $p = 0.30$ ). Among the pediatric cohort of 62 patients, the 5-year PFS for patients with chromosome 8 loss was 77.0% (95% CI 53.2–89.8) compared to 43.7% (95% CI 27.0–59.3) ( $p = 0.01$ ) (HR 0.3, 95% CI 0.1–0.8) (Online resource; Table 3, online resource). The association of chromosome 8 loss with survival advantage was not seen when the analysis was restricted to subtype VIII tumours.

Among Group 4 tumours, chromosome 11 loss nor 13q loss were predictive of outcomes (Online resource). Subtypes among Group 3 and Group 4 tumours were not predictive of survival (Online resource).

## Discussion

In our large international cohort of 191 adult medulloblastoma, we show that the individual subgroups and their subtypes display distinct clinical and biological heterogeneity. In exploratory analyses within subgroups, we identify copy number profiles which translate into specific prognostic features. Specifically, we report significantly worse PFS for SHH tumours with 3p loss, 10q loss, 17p loss, or *PTCH1* mutations and improved survival for Group 4 tumours with chromosome 8 loss. The latter finding was validated in an independent cohort of Group 4 tumours. Overall, these results suggest that cytogenetic risk stratification in adult medulloblastoma differs from that in children.

We did not establish any consistent clinical predictors such as age, sex, metastatic disease, or extent of resection which confirms the findings in other series [18, 37]. In our cohort, chemotherapy did not influence PFS which may contradict prior outcome studies [2–4]. One possibility is that the chemotherapy regimens differed between treatment sites and this heterogeneity may have limited a comprehensive comparison between groups, or alternatively the decision to administer chemotherapy was restricted to patients perceived to be higher risk. A number of international studies have reported survival advantages of chemotherapy following craniospinal irradiation [2–4, 8, 13, 14]. However, the tolerability of adjuvant pediatric chemotherapy in adults remains a concern, and requires urgent investigation in prospective cohorts [20].

Unlike medulloblastoma in children, risk classification strategies for medulloblastoma in adults are not well defined [27]. Similar to previous reports [37], we did not identify survival differences between the molecular subgroups. In particular, adult patients with WNT tumours do not have the excellent prognosis conferred to WNT pediatric tumours [6, 16, 27, 29]. *TP53* mutations are strongly prognostic among childhood SHH medulloblastoma [6]. The survival differences we report are limited by the low prevalence of *TP53* mutations despite a high prevalence of 17p loss in SHH; the role of 17p loss and its prognostic

significance requires further elucidation including evaluation at the protein level. Contrary to findings in children, *TP53* mutations are infrequently associated with genetic syndromes in adult medulloblastoma and more commonly represent somatic mutations; these differences between pediatric and adult tumours may explain the disparate prognostic significance [6, 7]. *TP53* mutations are also enriched in SHH $\alpha$ /SHH-3 and convey a poor prognosis, whereas in non-SHH $\alpha$ /SHH-3 prognostic significance has not been established [6, 20]. We did not observe any prognostic relevance of the two epigenetic subsets of the 106 SHH / SHH-4 cases in our multicenter cohort that were described by Korshunov et al. in a single institutional and uniformly treated cohort; however, consistent with this study, we observe VEGFA expression correlating significantly with outcome [18]. The cohorts were of similar size and were assigned using the same molecular classifier, yet we did not observe the same distributions of significant broad copy number changes (specifically 10q loss) and *PTCH1* mutations across the two adult SHH subtypes. Nevertheless, consistent with Korshunov et al. [18], we observed that 10q loss was a strong predictor of poor survival, which has not been observed in pediatric medulloblastoma [16, 19, 25]. Strikingly, we observe no prognostic value to 14q loss, in stark contrast to pediatric SHH medulloblastoma [33].

We report certain findings among Group 3 and 4 adult medulloblastoma which again show divergence from pediatric tumours. *MYC* and *MYCN* amplifications, respectively, seen in approximately 17% and 5% of pediatric medulloblastoma, respectively [24], were infrequently detected in Groups 3 and 4 tumours in this cohort as demonstrated in prior work [37]. Other pediatric markers of outcome in Group 4 such as whole chromosome 11 loss were not prognostic in our cohort, confirming that adult specific risk stratification is required [10]. Chromosome 8 loss, however, has been reported as enriched in Group 4 tumours in both children and adults [6, 10]. A survival advantage for pediatric patients with Group 4 tumours with chromosome 8 loss has been previously described by Goschzik et al. [10] which we were able to recapitulate in our pediatric cohort of 62 patients. Interestingly, we describe for the first time a notably improved survival in adult patients with Group 4 tumours with chromosome 8 loss compared to those with balanced chromosome 8, strengthened by validated findings in an independent cohort, which may allow for improved selection of adult Group 4 for intensification of therapy.

We have identified clinically relevant molecular prognosticators of adult medulloblastoma within molecular subgroups. Pediatric clinical trials have incorporated subgroup-specific treatment approaches to escalate or de-escalate therapy. Adult medulloblastoma patients may not benefit from such approaches based solely on subgroups but rather from trials which incorporate arm level or mutational events to establish risk groups. Through exploratory analyses we have identified high risk characteristics in adult SHH and protective events in Group 4 (chromosome 8 loss) medulloblastomas which may serve as a foundation for future risk-stratified prospective clinical trials. Limitations of our cohort include retrospective data, where patients were treated heterogeneously in numerous settings, which may have introduced bias when comparing treatment groups. Cases were collected predominantly from pediatric hospitals, where chemotherapy is more widely used for medulloblastoma treatment; this sampling may have biased our cohort towards a higher prevalence of chemotherapy use which may limit external validity. A limitation of our study is a lack of genome-wide sequencing with matched germline in adult Group 4 medulloblastoma, which

have a highly discrepant behavior from childhood Group 4. Considering the paucity of recurrent exonic somatic nucleotide variants in Group 4, it is critical that future prospective studies collect samples to allow for long-read sequencing for the discovery of both focal structural variants and nucleotide variants, including analysis of the germline [24].

Further elucidation of the prognostic markers and development of a robust risk stratification strategy for adult medulloblastoma will require international collaboration and validation given the rarity of this disease. However, future work of this neglected group should account for biological prognosticators in addition to molecular subgroups to achieve the same success as has been achieved for pediatric patients. Here we lay the foundation for the next generation of international clinical trials, of which there is an urgent and pressing need.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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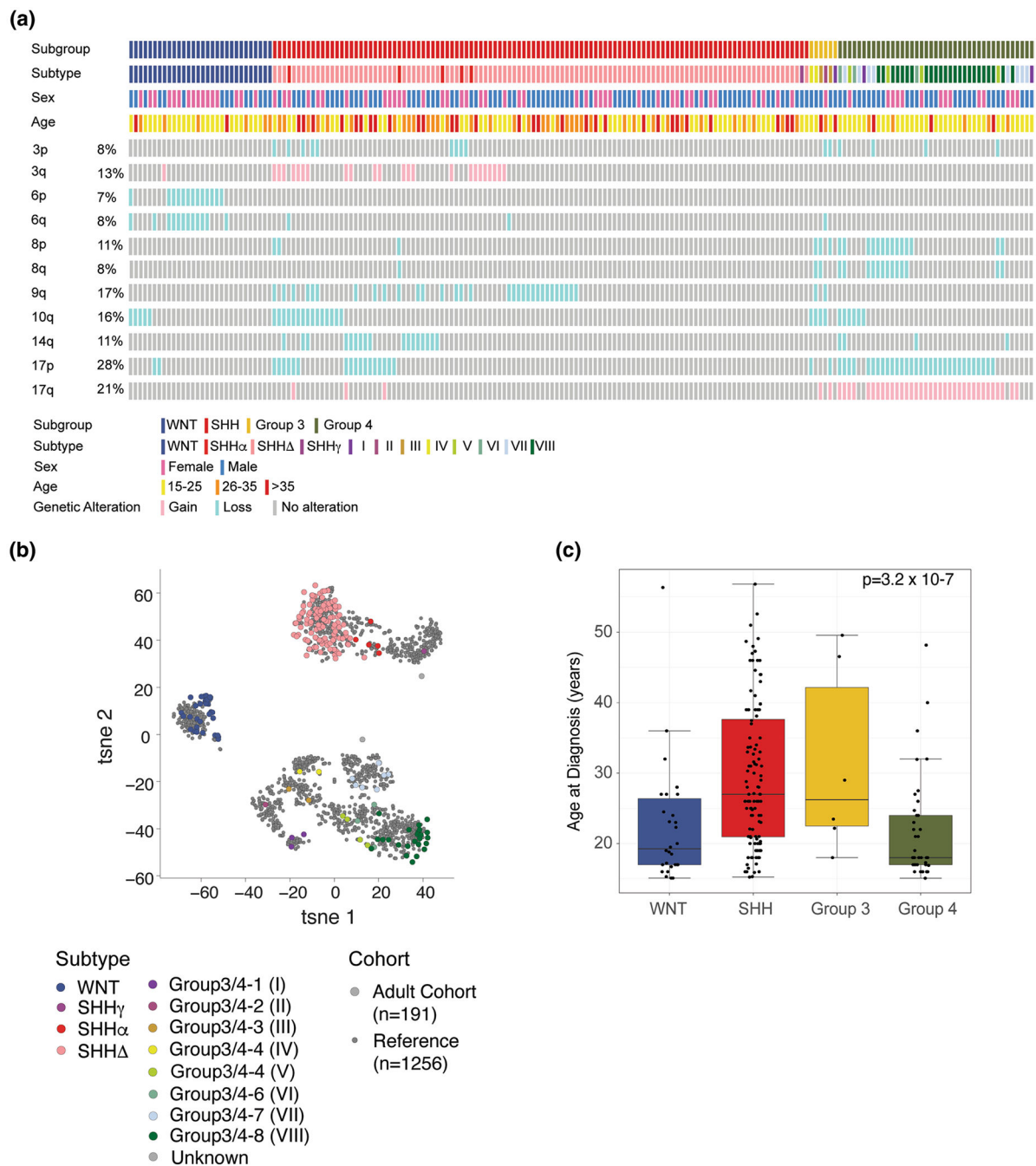
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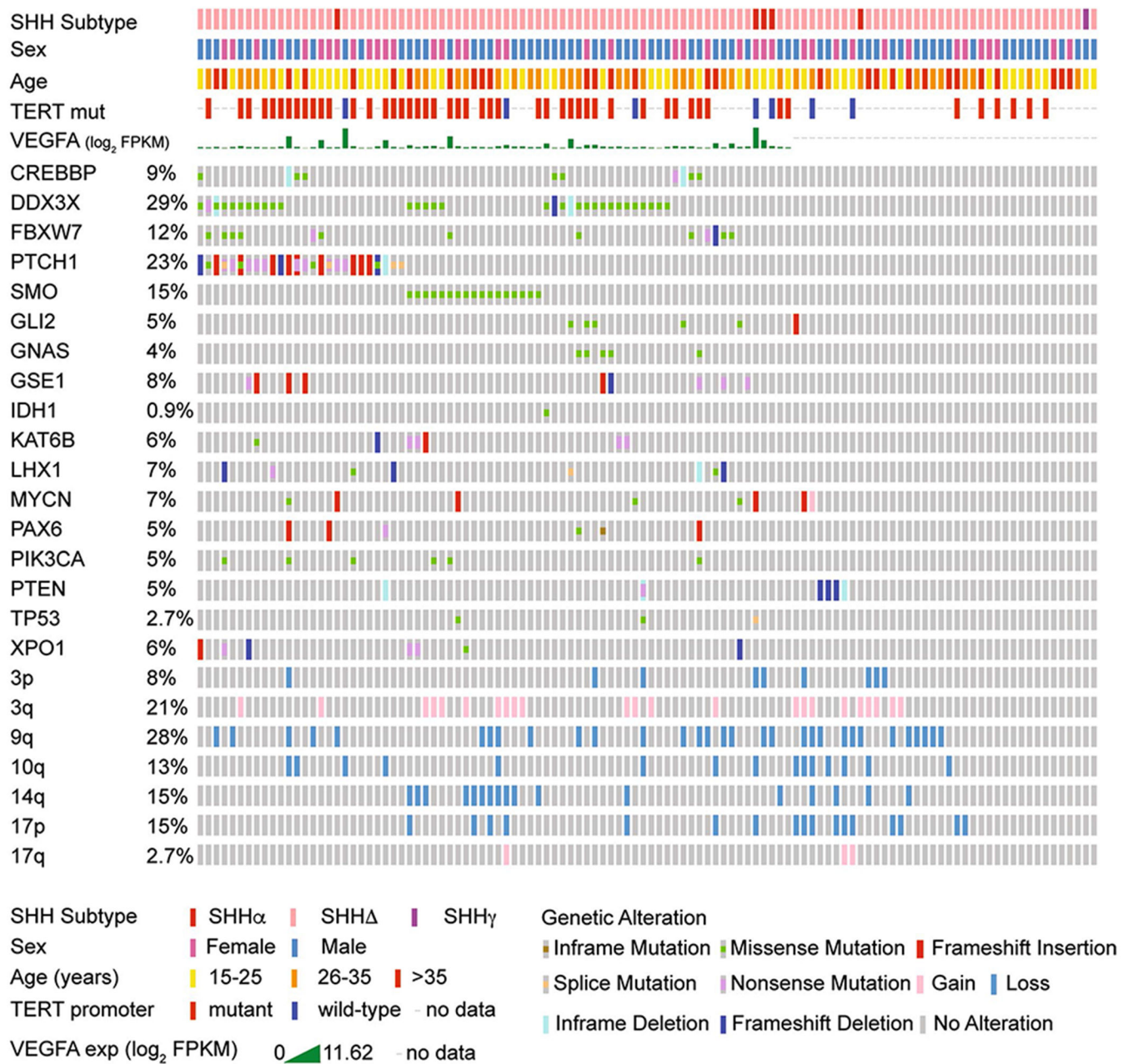
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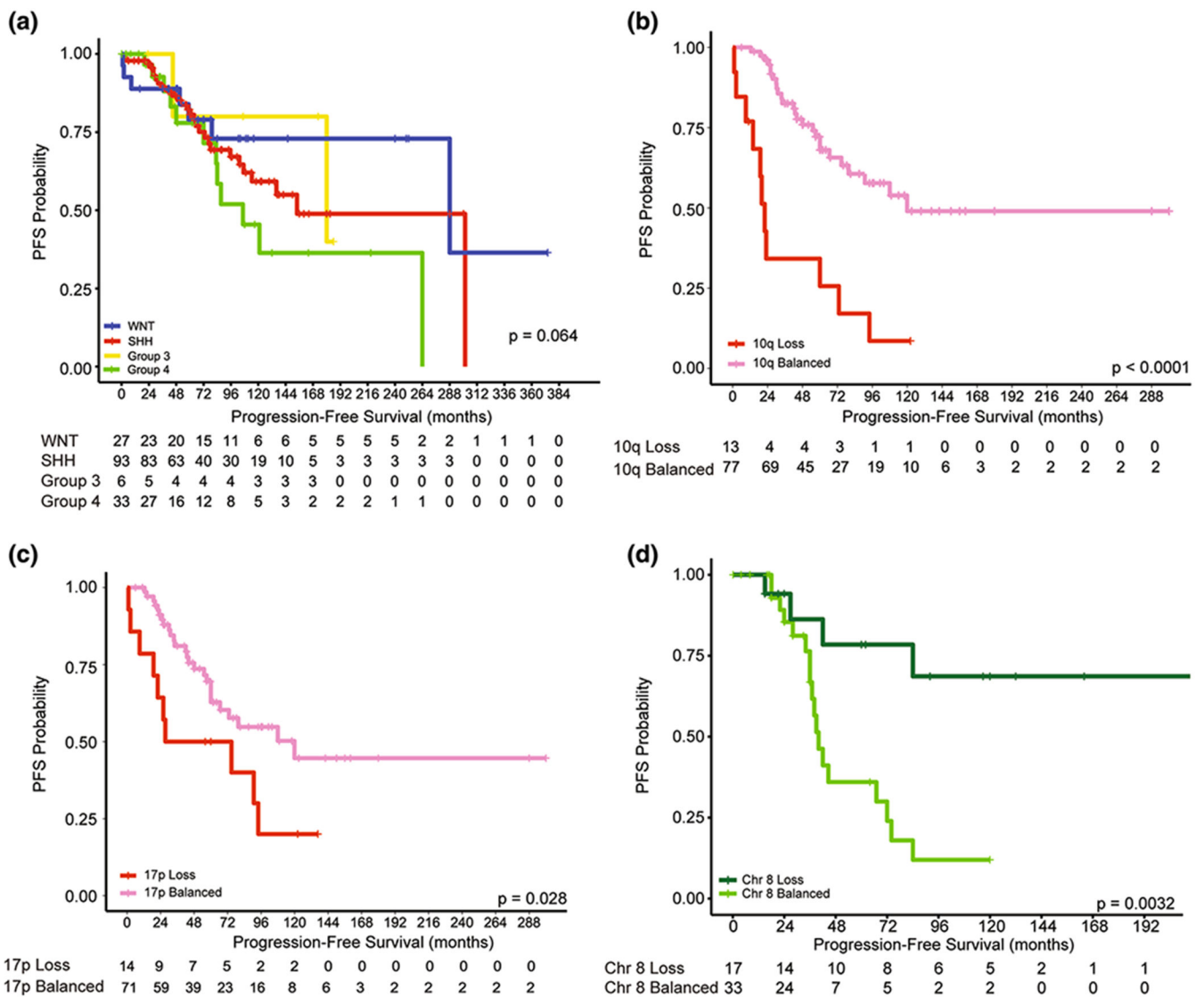


**Fig. 1.** Clinical and cytogenetic landscape of adult medulloblastoma. **a** Oncoprint depicting clinical characteristics, chromosomal aberrations and gene mutations of cohort. **b** Two-dimensional t-distributed stochastic neighbor embedding (t-SNE) plot demonstrating subtypes with reference cohort (Northcott et al. 2017). **c** Age distribution by subgroup ( $n = 189$ )



**Fig. 2.**  
Oncoprint depicting clinical characteristics, chromosomal aberrations, and gene mutations of SHH-activated medulloblastoma ( $n = 112$ )





**Fig. 3.** Survival analysis of adult medulloblastoma. Kaplan–Meier progression-free survival analysis of **a** Cohort by subgroup **b** 10q loss in adult SHH **c** 17p loss in adult SHH **d**) Chromosome 8 loss in Group 4 tumours.  $p$  value determined using the log-rank method

Table 1

## Demographic and clinical features of cohort

|                                | Total cohort (n = 191) |                  | WNT (n = 30)     | SHH (n = 112)   | Group 3 (n = 6)  | Group 4 (n = 41)   |
|--------------------------------|------------------------|------------------|------------------|---|--|--|
| Subtype (n, %) <sup>a</sup>    | N/A                    | N/A              | N/A              | Alpha3 5 (4.5)<br>Delta4 106 (94.6)<br>Gamma2 1 (0.9) | I/1 1 (16.7)<br>II/2 1 (16.7)<br>III/3 2 (33.3)<br>IV/4 2 (33.3) | I/1 2 (4.9)<br>V/5 4 (9.8)<br>VI/6 3 (7.3)<br>VII/7 8 (19.5)<br>VIII/8 24 (58.5)<br>18.0 (17.0–24.0) |
| Age at diagnosis (median, IQR) | 26.7 (18.0–32.0)       | 19.3 (17.0–27.0) | 27.0 (20.9–37.8) |   |  |  |
| Sex (n, %)                     |                        |                  |                  |   |  |  |
| Male                           | 118 (61.1)             | 14 (46.7)        | 70 (62.5)        |   | 5 (83.3)   | 27 (65.9)  |
| Female                         | 75 (38.9)              | 16 (53.3)        | 42 (37.5)        |   | 1 (16.7)   | 14 (34.1)  |
| Metastatic status              |                        |                  |                  |   |  |  |
| M0                             | 102 (80.9)             | 13 (72.2)        | 64 (87.7)        |   | 5 (100.0)  | 18 (64.3)  |
| M+                             | 24 (19.1)              | 5 (27.8)         | 9 (12.3)         |   | 0 (0.0)  | 10 (35.7)  |
| Extent of resection (n, %)     |                        |                  |                  |   |  |  |
| GTR/NTR                        | 107 (84.3)             | 20 (90.9)        | 52 (77.6)        |   | 5 (83.3)   | 28 (93.3)  |
| STR                            | 20 (15.7)              | 2 (9.1)          | 15 (22.4)        |   | 1 (16.7)   | 2 (6.7)  |
| Chemotherapy (n, %)            |                        |                  |                  |   |  |  |
| Yes                            | 95 (81.2)              | 12 (70.6)        | 53 (79.1)        |   | 4 (80.0)   | 24 (92.3)  |
| No                             | 22 (18.8)              | 5 (29.4)         | 14 (20.9)        |   | 1 (20.0)   | 2 (7.7)  |
| Radiation (n, %)               |                        |                  |                  |   |  |  |
| CSI with boost                 | 100 (93.5)             | 14 (87.5)        | 56 (94.9)        |   | 5 (100.0)  | 23 (92.0)  |
| Focal or WB                    | 7 (6.5)                | 2 (12.5)         | 3 (5.1)          |   | 0 (0.0)  | 2 (8.0)  |
| Relapses                       |                        |                  |                  |   |  |  |
| Local only                     | 17 (37.0)              | 3 (60.0)         | 10 (43.5)        |   | 1 (100.0)  | 2 (12.5)   |
| Metastatic                     | 29 (63.0)              | 2 (40.0)         | 13 (56.5)        |   | 0 (0.0)  | 14 (87.5)  |

Bold represents statistically significant variables  $p < 0.05$

CI 95% confidence interval; CSI/craniospinal irradiation; GTR gross total resection; IQR interquartile range; NA not applicable; M0 non metastatic; M+ metastatic; NTR near total resection; STR subtotal resection; WB whole brain

<sup>a</sup>Total of four patients could not be reliably subgrouped

Table 2

Univariate analysis of progression-free survival in adult medulloblastoma

| Variable                                     | Complete cohort (n = 154)        | WNT (n = 27)             | SHH (n = 90)                     | Groups 3 and 4 (n = 37)                     |
|--|----------------------------------|--------------------------|----------------------------------|---|
| Age over 25 years                            | 1.0 (0.6–1.6), p = 0.87          | 0.7 (0.1–3.3), p = 0.64  | 1.0 (0.5–2.0), p = 0.95          | 0.8 (0.3–2.5), p = 0.73                     |
| Male sex                                     | 0.7 (0.4–1.1), p = 0.13          | 1.2 (0.3–4.6), p = 0.75  | 0.7 (0.4–1.4), p = 0.30          | 0.3 (0.1–0.9), p = <b>0.02</b>              |
| Metastatic disease                           | 2.1 (1.0–4.0), p = <b>0.04</b>   | 2.3 (0.5–10.3), p = 0.30 | 1.5 (0.4–6.5), p = 0.57          | 2.7 (0.9–7.9), p = 0.07                     |
| Chemotherapy                                 | 0.7 (0.4–1.4), p = 0.31          | 0.4 (0.1–1.8), p = 0.20  | 0.8 (0.3–2.1), p = 0.70          | 0.7 (0.2–2.3), p = 0.52                     |
| Subtotal resection                           | 1.6 (0.8–3.3), p = 0.17          | 2.0 (0.2–16.4), p = 0.57 | 2.0 (0.8–4.8), p = 0.14          | 1.4 (0.3–6.2), p = 0.65                     |
| aSHH-MBI (versus aSHH-MBI)                   | N/A                              | N/A                      | 1.4 (0.7–2.7), p = 0.34          | N/A   |
| Group 3 and 4 subtype (ref I/1) <sup>c</sup> | N/A                              | N/A                      | N/A                              | N/A   |
| II/2   |                                  |                          |                                  | 2.5 (0.1–44.1)                              |
| III/3  |                                  |                          |                                  | N/A <sup>a</sup>                            |
| IV/4   |                                  |                          |                                  | N/A <sup>a</sup>                            |
| V/5  |                                  |                          |                                  | 7.1 (0.5–92.7)                              |
| VI/6   |                                  |                          |                                  | 1.2 (0.1–13.6)                              |
| VII/7  |                                  |                          |                                  | N/A <sup>a</sup>                            |
| VIII/8                                       |                                  |                          |                                  | 2.3 (0.3–18.4)                              |
| 1p loss                                      | 1.8 (0.3–13.1), p = 0.56         | 1.9 (0.3–13.9), p = 0.53 | N/A                              | N/A   |
| 1q gain                                      | 1.9 (0.8–4.3), p = 0.15          | N/A                      | N/A                              | N/A <sup>a</sup>                            |
| 3p loss                                      | 1.5 (0.7–3.5), p = 0.34          | N/A                      | 2.9 (1.1–7.6), p = <b>0.03</b>   | N/A   |
| 3q gain                                      | 1.3 (0.7–2.5), p = 0.47          | N/A                      | 1.5 (0.7–3.1), p = 0.27          | N/A   |
| Monosomy 6                                   | 0.4 (0.1–1.3), p = 0.14          | 0.5 (0.1–2.2), p = 0.39  | N/A                              | N/A   |
| Chr7 gain                                    | 0.6 (0.2–2.0), p = 0.44          | N/A                      | N/A                              | N/A   |
| Chr8 loss                                    | 0.7 (0.3–1.7), p = 0.42          | N/A                      | N/A                              | 0.2 (0.1–0.7), p = <b>0.007<sup>b</sup></b> |
| 9q loss                                      | 0.8 (0.4–1.6), p = 0.54          | N/A                      | 0.8 (0.4–1.8), p = 0.65          | N/A   |
| 10q loss                                     | 2.1 (1.2–3.6), p = <b>0.01</b>   | 2.5 (0.6–10.0), p = 0.20 | 4.6 (2.3–9.4), p < <b>0.0001</b> | 0.4 (0.1–1.3), p = 0.13                     |
| Chr11 loss                                   | 1.0 (0.4–2.5), p = 0.98          | N/A                      | N/A                              | 0.8 (0.2–3.6), p = 0.78 <sup>c</sup>        |
| 13q loss                                     | 1.9 (0.7–5.2), p = 0.21          | N/A                      | N/A                              | 0.9 (0.3–3.3), p = 0.92                     |
| 14q loss                                     | 0.7 (0.3–1.6), p = 0.40          | N/A                      | 0.8 (0.3–2.1), p = 0.64          | N/A   |
| 17p loss                                     | 2.4 (1.5–4.0), p = <b>0.0003</b> | N/A                      | 2.3 (1.1–4.8), p = <b>0.02</b>   | 2.4 (0.6–10.6), p = 0.23                    |

| Variable                                      | Complete cohort (n = 154)        | WNT (n = 27) | SHH (n = 90)                      | Groups 3 and 4 (n = 37)         |
|---|----------------------------------|--------------|-----------------------------------|---------------------------------|
| 17q gain                                      | 1.7 (1.0–2.9), <b>p = 0.0475</b> | N/A          | 1.7 (0.4–7.2), <b>p = 0.46</b>    | 1.7 (0.4–7.2), <b>p = 0.50</b>  |
| Iso17q  | 1.9 (1.1–3.2), <b>p = 0.02</b>   | N/A          | N/A                               | 2.5 (0.6–11.0), <b>p = 0.22</b> |
| Chr20 loss                                    | 1.0 (0.2–3.9), <b>p = 0.96</b>   | N/A          | N/A                               | N/A                             |
| <i>PTCH1</i> mutation                         | N/A                              | N/A          | 2.4 (1.1–5.4), <b>p = 0.04</b>    | N/A                             |
| <i>TP53</i> mutation                          | N/A                              | N/A          | 10.8 (2.3–50.9), <b>p = 0.003</b> | N/A                             |
| <i>VEGFA</i> expression <sup>d</sup>          | N/A                              | N/A          | N/A                               | N/A                             |
| 0.54–0.78                                     |                                  |              | 0.4 (0.1–1.8)                     |                                 |
| 0.78–1.2                                      |                                  |              | 1.6 (0.5–4.9)                     |                                 |
| 1.2 <sup>+</sup>                              |                                  |              | 1.1 (0.3–3.7)                     |                                 |
| <i>VEGFA</i> expression (per 1 FPKM increase) | N/A                              | N/A          | 1.2 (1.0–1.5), <b>p = 0.02</b>    | N/A                             |
| <i>U1</i> mutation                            | N/A                              | N/A          | 0.4 (0.1–1.5), <b>p = 0.17</b>    | N/A                             |

Bold represents statistically significant variables  $p < 0.05$

<sup>+</sup> and over; *Chr* chromosome; *HR* hazard ratio; *NA* not applicable; *SHH* Sonic Hedgehog; *ref* reference

<sup>a</sup> Too few cases to compute estimate

<sup>b</sup> Only Group 4 cases (n = 59)

<sup>c</sup> Only Group 4 cases (n = 31), *p* value = 0.85

<sup>d</sup> Reference: 0.54–0.78

**Table 3**

Multivariable analysis of progression-free survival in adult SHH medulloblastoma

| Variable           | Hazard Ratio | 95% CI   | p value      |
|--------------------|--------------|----------|--------------|
| Age over 25 years  | 1.5          | 0.6–3.8  | 0.38         |
| Metastatic disease | 1.8          | 0.4–8.7  | 0.49         |
| Subtotal resection | 1.7          | 0.7–4.4  | 0.25         |
| 3p loss            | 3.4          | 1.1–11.0 | <b>0.04</b>  |
| 10q loss           | 5.0          | 1.9–13.2 | <b>0.001</b> |
| 14q loss           | 0.9          | 0.2–3.7  | 0.92         |
| 17p loss           | 3.2          | 1.0–10.3 | 0.05         |

Bold represents statistically significant variables  $p < 0.05$ 

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