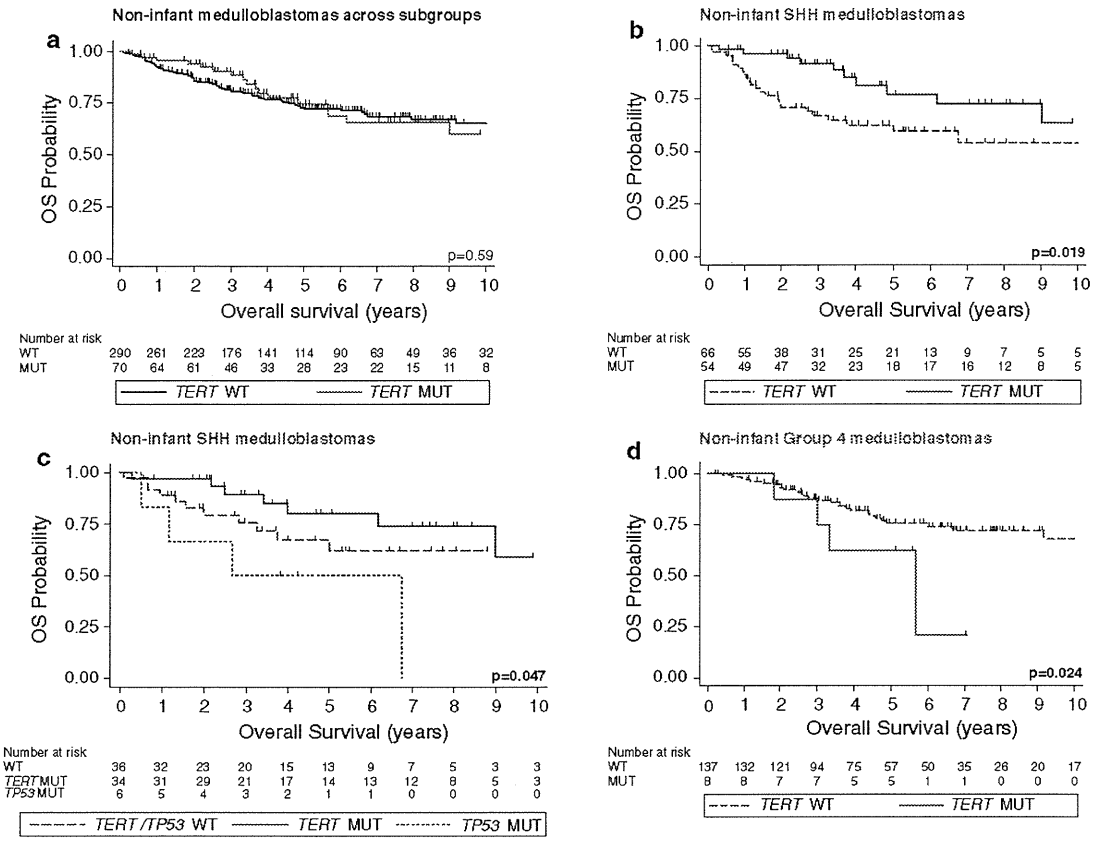


Fig. 3 *TERT* promoter mutations delineate prognostic subsets within non-infant SHH and Group 4 medulloblastomas. Kaplan–Meier estimate displaying overall survival (OS) in non-infant medulloblastomas (>3 years of age at diagnosis) according to *TERT* mutational status across subgroups (**a**), in SHH tumors (**b**), in SHH tumors (*TP53* mutated/wild-type) (**c**), and Group 4 (**d**). Survival differences were calculated using continuous log-rank tests

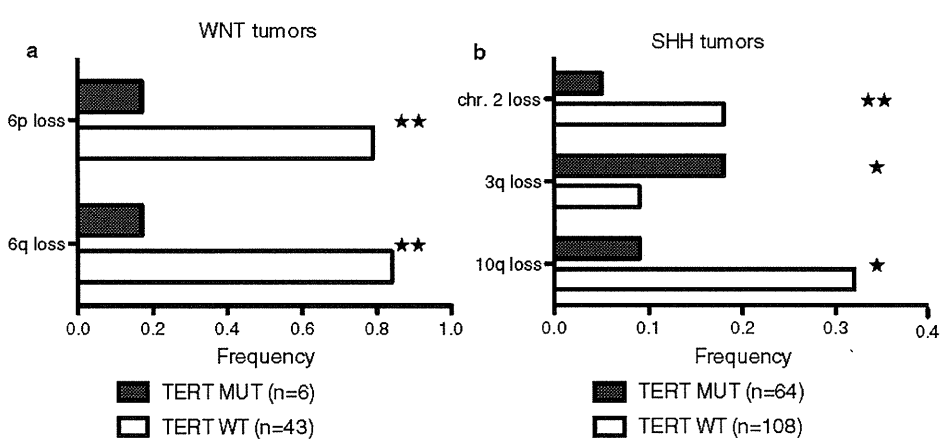
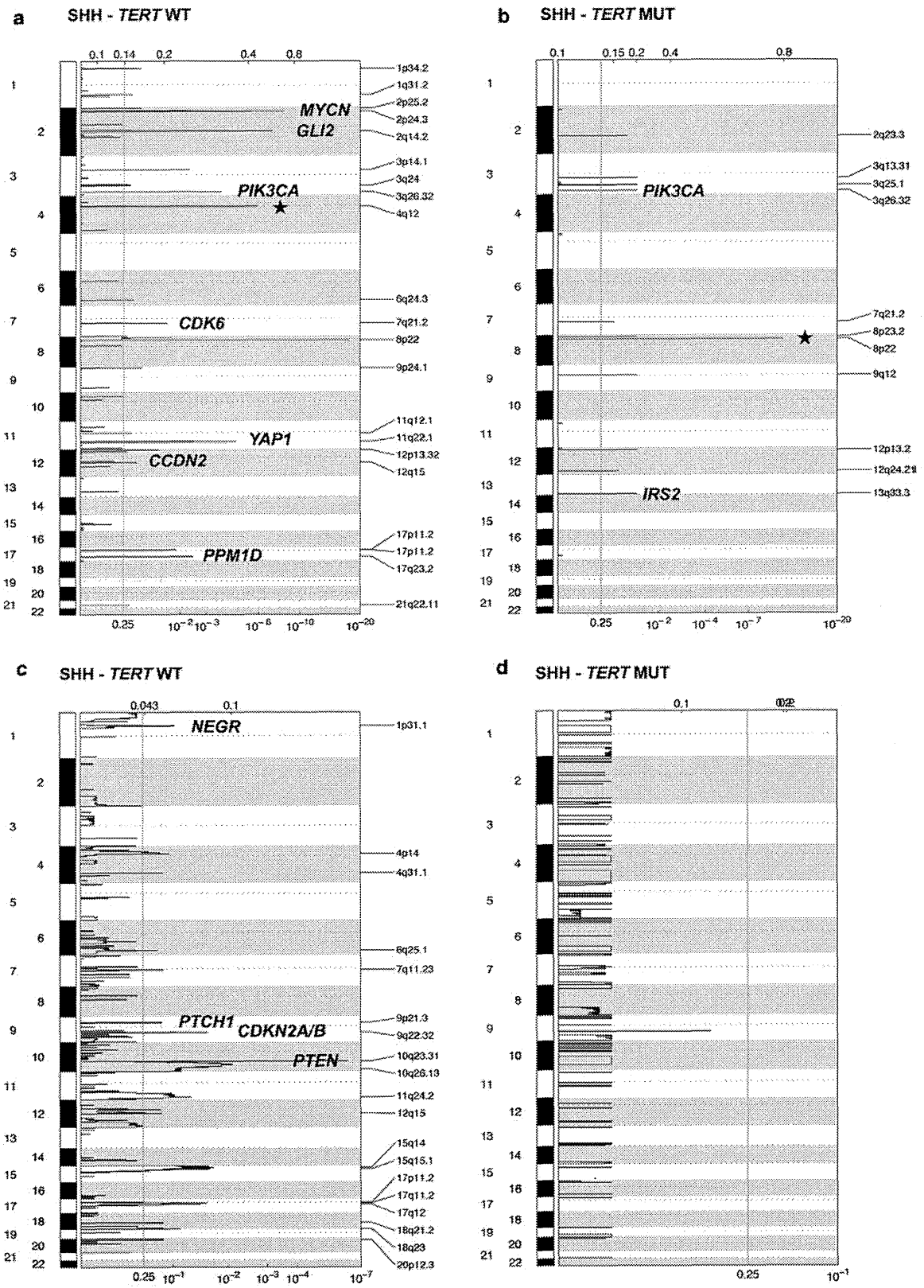


Fig. 4 WNT and SHH medulloblastoma harbor distinct broad genomic imbalances depending on the mutational status of *TERT*. *Bar graphs* indicating the frequency of broad cytogenetic alterations in WNT (**a**), and SHH (**b**) tumors. ★★ $p < 0.01$; ★ $p < 0.05$; *MUT* mutation, *WT* wild-type

recurrent *TERT* promoter mutations makes a compelling argument that the increasing availability of whole-genome sequencing results may substantially add to a refined understanding of the mutational landscape of different biological and age-driven medulloblastoma subgroups, since earlier next-generation sequencing studies focusing on the protein-coding regions had not encompassed gene-regulatory regions including promoter mutations.

In this study, we demonstrate that the mutational status of the *TERT* promoter can segregate individuals with SHH


a
SHH - TERT WT
MYCN
GLI2
PIK3CA
CDK6
YAP1
CCDN2
PPM1D
b
SHH - TERT MUT
PIK3CA
IRS2
c
SHH - TERT WT
NEGR
PTCH1
CDKN2A/B
PTEN
d
SHH - TERT MUT

◂**Fig. 5** Focal somatic copy number alterations are largely confined to *TERT* wild-type SHH medulloblastomas. GISTIC2 analysis indicating focal amplifications/deletions in 108 wild-type (**a**, **c**) and 64 mutant (**b**, **d**) SHH tumors, respectively. *Star* regions enriched for reported DNA copy number variations

and Group 4 medulloblastomas with distinct prognostic outcomes, while a prognostic impact of this mutation was not observed in glioblastomas [23]. Molecular mechanisms converging on *TERT* up-regulation were recently reported to be associated with dismal prognosis in pediatric brain cancers [4]. Our findings in Group 4 tumors with *TERT* mutations follow this pattern, while SHH tumors with *TERT* mutations comprise a prognostically favorable subgroup. Notably, survival curves of SHH tumors increasingly approximate with extended follow-up. We hypothesize that this pattern might be due to secondary malignancies and late relapses in older SHH tumors [36–38]. Since virtually all of the *TERT* promoter mutations encompass the mutational hotspots C228T and C250T, patient stratification can be carried out using a single PCR followed up with Sanger sequencing or with a single experiment using our newly designed Taqman-based genotyping assay. The latter assay is particularly suitable for routine clinical applications as it is highly sensitive and specific (5 ng DNA input is sufficient). Furthermore, our Taqman-based genotyping assay can be used on DNA derived from fresh-frozen and formalin-fixed paraffin-embedded tissue, since it only amplifies a short DNA fragment.

Both hotspot mutations C228T and C250T create an E-twenty-six (ETS) binding motif [10, 11] resulting in up-regulation of *TERT* expression at the mRNA level [2], which was not observed at the protein level in glioblastomas [43]. We now demonstrate that SHH tumors with *TERT* mutations are mostly mutually exclusive with those harboring 10q loss ($p = 0.017$) Notably, the relatively favorable prognosis of *TERT*-mutated SHH medulloblastomas may be explained by the relative lack of high-risk biomarkers [17, 18, 24, 44].

In summary, we describe the demographic, clinicopathological, and biological implications of *TERT* promoter mutations in a subgroup-specific fashion. This study underlines the dependence of adult WNT and SHH tumors to reacquire telomerase activity and suggests a potential prognostic utility of *TERT* mutational analysis in an era of individualized therapy.

Acknowledgments We thank Susan Archer for technical writing, and Nick Downey from Integrated DNA Technologies for support with probe/primer design. We acknowledge CRB HCL—Neurobiotec tumor bank (Hospices Civils de Lyon, Lyon, France). MDT is supported by a CIHR Clinician Scientist Phase II award, funds from the Garron Family Chair in Childhood Cancer Research at The Hospital for Sick Children and the University of Toronto, and operating funds from the Canadian Institutes of Health Research, the National Institutes of Health (R01CA159859 and R01CA148699) and the Pediatric Brain Tumor Foundation. MR is supported by a fellowship from the Dr. Mildred Scheel Foundation for Cancer Research/German Cancer Aid and funds from the Baden-Wurttemberg Foundation. VR is supported by a CIHR fellowship and an Alberta Innovates-Health Solutions Clinical Fellowship. KZ acknowledges research support from MH CZ-DRO FNBr 65269705. AK was supported by the TAMOP-4.2.2A-11/1/KONV-2012-0025 project and the János Bolyai Scholarship of the Hungarian Academy of Sciences.

Conflict of interest The authors declare no conflicts of interest.

References

1. Aaron RH, Elion GB, Colvin OM, Graham M, Keir S, Bigner DD, Friedman HS (1994) Busulfan therapy of central nervous system xenografts in athymic mice. Cancer Chemother Pharmacol 35(2):127–131
2. Arita H, Narita Y, Fukushima S, Tateishi K, Matsushita Y, Yoshida A, Miyakita Y, Ohno M, Collins VP, Kawahara N, Shibui S, Ichimura K (2013) Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. Acta Neuropathol 126(2):267–276. doi:10.1007/s00401-013-1141-6
3. Blasco MA (2005) Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet 6(8):611–622. doi:10.1038/nrg1656
4. Castelo-Branco P, Choufani S, Mack S, Gallagher D, Zhang C, Lipman T, Zhukova N, Walker EJ, Martin D, Merino D, Wasserman JD, Elizabeth C, Alon N, Zhang L, Hovestadt V, Kool M, Jones DT, Zadeh G, Croul S, Hawkins C, Hitzler J, Wang JC, Baruchel S, Dirks PB, Malkin D, Pfister S, Taylor MD, Weksberg R, Tabori U (2013) Methylation of the TERT promoter and risk stratification of childhood brain tumours: an integrative genomic and molecular study. Lancet Oncol 14(6):534–542. doi:10.1016/S1470-2045(13)70110-4
5. Cho YJ, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, Berhoukim R, Amani V, Goumnerova L, Eberhart CG, Lau CC, Olson JM, Gilbertson RJ, Gajjar A, Delattre O, Kool M, Ligon K, Meyerson M, Mesirov JP, Pomeroy SL (2011) Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol 29(11):1424–1430. doi:10.1200/JCO.2010.28.5148
6. Dubuc AM, Northcott PA, Mack S, Witt H, Pfister S, Taylor MD (2010) The genetics of pediatric brain tumors. Curr Neurol Neurosci Rep 10(3):215–223. doi:10.1007/s11910-010-0103-9
7. Forsyth NR, Wright WE, Shay JW (2002) Telomerase and differentiation in multicellular organisms: turn it off, turn it on, and turn it off again. Differentiation 69(4–5):188–197. doi:10.1046/j.1432-0436.2002.690412.x
8. Heaphy CM, Subhawong AP, Hong SM, Goggins MG, Montgomery EA, Gabrielson E, Netto GJ, Epstein JI, Lotan TL, Westra WH, Shih Ie M, Iacobuzio-Donahue CA, Maitra A, Li QK, Eberhart CG, Taube JM, Rakheja D, Kurman RJ, Wu TC, Roden RB, Argani P, De Marzo AM, Terracciano L, Torbenson M, Meeker AK (2011) Prevalence of the alternative lengthening of telomeres telomere maintenance mechanism in human cancer subtypes. Am J Pathol 179(4):1608–1615. doi:10.1016/j.ajpath.2011.06.018

9. Hiyama E, Hiyama K (2007) Telomere and telomerase in stem cells. Br J Cancer 96(7):1020–1024. doi:10.1038/sj.bjc.6603671
10. Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, Gast A, Kadel S, Moll I, Nagore E, Hemminki K, Schadendorf D, Kumar R (2013) TERT promoter mutations in familial and sporadic melanoma. Science 339(6122):959–961. doi:10.1126/science.1230062
11. Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA (2013) Highly recurrent TERT promoter mutations in human melanoma. Science 339(6122):957–959. doi:10.1126/science.1229259
12. Jones DT, Jager N, Kool M, Zichner T, Hutter B, Sultan M, Cho YJ, Pugh TJ, Hovestadt V, Stutz AM, Rausch T, Warnatz HJ, Ryzhova M, Bender S, Sturm D, Pleier S, Cin H, Pfaff E, Sieber L, Wittmann A, Remke M, Witt H, Hutter S, Tzaridis T, Weischenfeldt J, Raeder B, Avci M, Amstislavskiy V, Zapatka M, Weber UD, Wang Q, Lasitschka B, Bartholomae CC, Schmidt M, von Kalle C, Ast V, Lawerenz C, Eils J, Kabbe R, Benes V, van Sluis P, Koster J, Volckmann R, Shih D, Betts MJ, Russell RB, Coco S, Tonini GP, Schuller U, Hans V, Graf N, Kim YJ, Monoranu C, Roggendorf W, Unterberg A, Herold-Mende C, Milde T, Kulozik AE, von Deimling A, Witt O, Maass E, Rossler J, Ebinger M, Schuhmann MU, Fruhwald MC, Hasselblatt M, Jabado N, Rutkowski S, von Bueren AO, Williamson D, Clifford SC, McCabe MG, Collins VP, Wolf S, Wiemann S, Lehrach H, Brors B, Scheurlen W, Felsberg J, Reifenberger G, Northcott PA, Taylor MD, Meyerson M, Pomeroy SL, Yaspo ML, Korbel JO, Korshunov A, Eils R, Pfister SM, Lichter P (2012) Dissecting the genomic complexity underlying medulloblastoma. Nature 488(7409):100–105. doi:10.1038/nature11284
13. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA Jr, Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih Ie M, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H (2013) TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA 110(15):6021–6026. doi:10.1073/pnas.1303607110
14. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, Coviello GM, Wright WE, Weinrich SL, Shay JW (1994) Specific association of human telomerase activity with immortal cells and cancer. Science 266(5193):2011–2015
15. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA, Cho YJ, Koster J, Schouten-van Meeteren A, van Vuurden D, Clifford SC, Pietsch T, von Bueren AO, Rutkowski S, McCabe M, Collins VP, Backlund ML, Haberler C, Bourdeaut F, Delattre O, Doz F, Ellison DW, Gilbertson RJ, Pomeroy SL, Taylor MD, Lichter P, Pfister SM (2012) Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 123(4):473–484. doi:10.1007/s00401-012-0958-8
16. Kool M, Koster J, Bunt J, Hasselt NE, Lakeman A, van Sluis P, Troost D, Meeteren NS, Caron HN, Cloos J, Mrsic A, Ylstra B, Grajkowska W, Hartmann W, Pietsch T, Ellison D, Clifford SC, Versteeg R (2008) Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. PLoS One 3(8):e3088. doi:10.1371/journal.pone.0003088
17. Korshunov A, Remke M, Kool M, Hielscher T, Northcott PA, Williamson D, Pfaff E, Witt H, Jones DT, Ryzhova M, Cho YJ, Wittmann A, Benner A, Weiss WA, von Deimling A, Scheurlen W, Kulozik AE, Clifford SC, Peter Collins V, Westermann F, Taylor MD, Lichter P, Pfister SM (2012) Biological and clinical heterogeneity of MYCN-amplified medulloblastoma. Acta Neuropathol 123(4):515–527. doi:10.1007/s00401-011-0918-8
18. Korshunov A, Remke M, Werft W, Benner A, Ryzhova M, Witt H, Sturm D, Wittmann A, Schottler A, Felsberg J, Reifenberger G, Rutkowski S, Scheurlen W, Kulozik AE, von Deimling A, Lichter P, Pfister SM (2010) Adult and pediatric medulloblastomas are genetically distinct and require different algorithms for molecular risk stratification. J Clin Oncol 28(18):3054–3060. doi:10.1200/JCO.2009.25.7121
19. Liu X, Bishop J, Shan Y, Pai S, Liu D, Murugan AK, Sun H, El-Naggar AK, Xing M (2013) Highly prevalent TERT promoter mutations in aggressive thyroid cancers. Endocr Relat Cancer 20(4):603–610. doi:10.1530/ERC-13-0210
20. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114(2):97–109. doi:10.1007/s00401-007-0243-4
21. Mermel CH, Schumacher SE, Hill B, Meyerson ML, Beroukhim R, Getz G (2011) GISTIC2.0 facilitates sensitive and confident localization of the targets of focal somatic copy-number alteration in human cancers. Genome Biol 12(4):R41. doi:10.1186/gb-2011-12-4-r41
22. Morrison SJ, Prowse KR, Ho P, Weissman IL (1996) Telomerase activity in hematopoietic cells is associated with self-renewal potential. Immunity 5(3):207–216
23. Nonoguchi N, Ohta T, Oh JE, Kim YH, Kleihues P, Ohgaki H (2013) TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol. doi:10.1007/s00401-013-1163-0
24. Northcott PA, Hielscher T, Dubuc A, Mack S, Shih D, Remke M, Al-Halabi H, Albrecht S, Jabado N, Eberhart CG, Grajkowska W, Weiss WA, Clifford SC, Bouffet E, Rutka JT, Korshunov A, Pfister S, Taylor MD (2011) Pediatric and adult sonic hedgehog medulloblastomas are clinically and molecularly distinct. Acta Neuropathol 122(2):231–240. doi:10.1007/s00401-011-0846-7
25. Northcott PA, Jones DT, Kool M, Robinson GW, Gilbertson RJ, Cho YJ, Pomeroy SL, Korshunov A, Lichter P, Taylor MD, Pfister SM (2012) Medulloblastomics: the end of the beginning. Nat Rev Cancer 12(12):818–834. doi:10.1038/nrc3410
26. Northcott PA, Korshunov A, Pfister SM, Taylor MD (2012) The clinical implications of medulloblastoma subgroups. Nat Rev Neurol 8(6):340–351. doi:10.1038/nrneurol.2012.78
27. Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S, Bouffet E, Clifford SC, Hawkins CE, French P, Rutka JT, Pfister S, Taylor MD (2011) Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 29(11):1408–1414. doi:10.1200/JCO.2009.27.4324
28. Northcott PA, Nakahara Y, Wu X, Feuk L, Ellison DW, Croul S, Mack S, Kongkham PN, Peacock J, Dubuc A, Ra YS, Zilberberg K, McLeod J, Scherer SW, Sunil Rao J, Eberhart CG, Grajkowska W, Gillespie Y, Lach B, Grundy R, Pollack IF, Hamilton RL, Van Meter T, Carlotti CG, Boop F, Bigner D, Gilbertson RJ, Rutka JT, Taylor MD (2009) Multiple recurrent genetic events converge on control of histone lysine methylation in medulloblastoma. Nat Genet 41(4):465–472. doi:10.1038/ng.336
29. Northcott PA, Rutka JT, Taylor MD (2010) Genomics of medulloblastoma: from Giemsa-banding to next-generation sequencing in 20 years. Neurosurg Focus 28(1):E6. doi:10.3171/2009.10.FOCUS09218
30. Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stutz AM, Korshunov A, Reimand J, Schumacher SE, Beroukhim R, Ellison DW, Marshall CR, Lionel AC, Mack S, Dubuc A, Yao Y, Ramaswamy V, Luu B, Rolider A, Cavalli FM, Wang X, Remke M, Wu X, Chiu RY, Chu A, Chuah E, Corbett RD, Hoad GR, Jackman SD, Li Y, Lo A, Mungall KL, Nip KM, Qian JQ, Raymond AG, Thiessen NT, Varhol RJ, Birol I, Moore

RA, Mungall AJ, Holt R, Kawauchi D, Roussel MF, Kool M, Jones DT, Witt H, Fernandez LA, Kenney AM, Wechsler-Reya RJ, Dirks P, Aviv T, Grajkowska WA, Perek-Polnik M, Haberler CC, Delattre O, Reynaud SS, Doz FF, Pernet-Fattet SS, Cho BK, Kim SK, Wang KC, Scheurlen W, Eberhart CG, Fevre-Montange M, Jouvet A, Pollack IF, Fan X, Muraszko KM, Gillespie GY, Di Rocco C, Massimi L, Michiels EM, Kloosterhof NK, French PJ, Kros JM, Olson JM, Ellenbogen RG, Zitterbart K, Kren L, Thompson RC, Cooper MK, Lach B, McLendon RE, Bigner DD, Fontebasso A, Albrecht S, Jabado N, Lindsey JC, Bailey S, Gupta N, Weiss WA, Bognar L, Klekner A, Van Meter TE, Kumabe T, Tominaga T, Elbabaa SK, Leonard JR, Rubin JB, Liau LM, Van Meir EG, Fouladi M, Nakamura H, Cinalli G, Garami M, Hauser P, Saad AG, Iolascon A, Jung S, Carlotti CG, Vibhakar R, Ra YS, Robinson S, Zollo M, Faria CC, Chan JA, Levy ML, Sorensen PH, Meyerson M, Pomeroy SL, Cho YJ, Bader GD, Tabori U, Hawkins CE, Bouffet E, Scherer SW, Rutka JT, Malkin D, Clifford SC, Jones SJ, Korbel JO, Pfister SM, Marra MA, Taylor MD (2012) Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 488(7409):49–56. doi:10.1038/nature11327

31. Northcott PA, Shih DJ, Remke M, Cho YJ, Kool M, Hawkins C, Eberhart CG, Dubuc A, Guettouche T, Cardentey Y, Bouffet E, Pomeroy SL, Marra M, Malkin D, Rutka JT, Korshunov A, Pfister S, Taylor MD (2011) Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. Acta Neuropathol. doi:10.1007/s00401-011-0899-7
32. Parsons DW, Li M, Zhang X, Jones S, Leary RJ, Lin JC, Boca SM, Carter H, Samayoa J, Bettegowda C, Gallia GL, Jallo GI, Binder ZA, Nikolsky Y, Hartigan J, Smith DR, Gerhard DS, Fults DW, VandenBerg S, Berger MS, Marie SK, Shinjo SM, Clara C, Phillips PC, Minturn JE, Biegel JA, Judkins AR, Resnick AC, Storm PB, Curran T, He Y, Rasheed BA, Friedman HS, Keir ST, McLendon R, Northcott PA, Taylor MD, Burger PC, Riggins GJ, Karchin R, Parmigiani G, Bigner DD, Yan H, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE (2011) The genetic landscape of the childhood cancer medulloblastoma. Science 331(6016):435–439. doi:10.1126/science.1198056
33. Pfister SM, Korshunov A, Kool M, Hasselblatt M, Eberhart C, Taylor MD (2010) Molecular diagnostics of CNS embryonal tumors. Acta Neuropathol 120(5):553–566. doi:10.1007/s00401-010-0751-5
34. Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, Bochicchio J, Carneiro MO, Carter SL, Cibulskis K, Erlich RL, Greulich H, Lawrence MS, Lennon NJ, McKenna A, Meldrim J, Ramos AH, Ross MG, Russ C, Shefler E, Sivachenko A, Sogoloff B, Stojanov P, Tamayo P, Mesirov JP, Amani V, Teider N, Sengupta S, Francois JP, Northcott PA, Taylor MD, Yu F, Crabtree GR, Kautzman AG, Gabriel SB, Getz G, Jager N, Jones DT, Lichter P, Pfister SM, Roberts TM, Meyerson M, Pomeroy SL, Cho YJ (2012) Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. Nature 488(7409):106–110. doi:10.1038/nature11329
35. Ramaswamy V, Northcott PA, Taylor MD (2011) FISH and chips: the recipe for improved prognostication and outcomes for children with medulloblastoma. Cancer Genet 204(11):577–588. doi:10.1016/j.cancergen.2011.11.001
36. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, Shih DJ, Luu B, Dubuc AM, Northcott PA, Schüller U, Gururangan S, McLendon R, Bigner D, Fouladi M, Ligon KL, Pomeroy SL, Dunn S, Triscott J, Jabado N, Fontebasso A, Jones DT, Kool M, Karajannis MA, Gardner SL, Zagzag D, Nunes S, Pimentel J, Mora J, Lipp E, Walter AW, Ryzhova M, Zheludkova O, Kumirova E, Alshami J, Croul SE, Rutka JT, Hawkins C, Tabori U, Codispoti KE, Packer RJ, Pfister SM, Korshunov A, Taylor MD (2013) Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol. doi:10.1016/S1470-2045(13)70449-2
37. Remke M, Hielscher T, Korshunov A, Northcott PA, Bender S, Kool M, Westermann F, Benner A, Cin H, Ryzhova M, Sturm D, Witt H, Haag D, Toedt G, Wittmann A, Schottler A, von Bueren AO, von Deimling A, Rutkowski S, Scheurlen W, Kulozik AE, Taylor MD, Lichter P, Pfister SM (2011) FSTL5 Is a marker of poor prognosis in Non-WNT/Non-SHH medulloblastoma. J Clin Oncol 29(29):3852–3861. doi:10.1200/JCO.2011.36.2798
38. Remke M, Hielscher T, Northcott PA, Witt H, Ryzhova M, Wittmann A, Benner A, von Deimling A, Scheurlen W, Perry A, Croul S, Kulozik AE, Lichter P, Taylor MD, Pfister SM, Korshunov A (2011) Adult medulloblastoma comprises three major molecular variants. J Clin Oncol 29(19):2717–2723. doi:10.1200/JCO.2011.34.9373
39. Robinson G, Parker M, Kranenburg TA, Lu C, Chen X, Ding L, Phoenix TN, Hedlund E, Wei L, Zhu X, Chalhoub N, Baker SJ, Huether R, Kriwacki R, Curley N, Thiruvenkatam R, Wang J, Wu G, Rusch M, Hong X, Becksfort J, Gupta P, Ma J, Easton J, Vadodaria B, Onar-Thomas A, Lin T, Li S, Pounds S, Paugh S, Zhao D, Kawauchi D, Roussel MF, Finkelstein D, Ellison DW, Lau CC, Bouffet E, Hassall T, Gururangan S, Cohn R, Fulton RS, Fulton LL, Dooling DJ, Ochoa K, Gajjar A, Mardis ER, Wilson RK, Downing JR, Zhang J, Gilbertson RJ (2012) Novel mutations target distinct subgroups of medulloblastoma. Nature 488(7409):43–48. doi:10.1038/nature11213
40. Rutkowski S, von Hoff K, Emser A, Zwiener I, Pietsch T, Figarella-Branger D, Giangaspero F, Ellison DW, Garre ML, Biassoni V, Grundy RG, Finlay JL, Dhall G, Raquin MA, Grill J (2010) Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. J Clin Oncol 28(33):4961–4968. doi:10.1200/JCO.2010.30.2299
41. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123(4):465–472. doi:10.1007/s00401-011-0922-z
42. Thompson MC, Fuller C, Hogg TL, Dalton J, Finkelstein D, Lau CC, Chintagumpala M, Adesina A, Ashley DM, Kellie SJ, Taylor MD, Curran T, Gajjar A, Gilbertson RJ (2006) Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol 24(12):1924–1931. doi:10.1200/JCO.2005.04.4974
43. Vinagre J, Almeida A, Populo H, Batista R, Lyra J, Pinto V, Coelho R, Celestino R, Prazeres H, Lima L, Melo M, Rocha AG, Preto A, Castro P, Castro L, Pardal F, Lopes JM, Santos LL, Reis RM, Cameselle-Teijeiro J, Sobrinho-Simoes M, Lima J, Maximo V, Soares P (2013) Frequency of TERT promoter mutations in human cancers. Nature Commun 4:2185. doi:10.1038/ncomms3185
44. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC, Castelo-Branco P, Baskin B, Ray PN, Bouffet E, von Bueren AO, Jones DT, Northcott PA, Kool M, Sturm D, Pugh TJ, Pomeroy SL, Cho YJ, Pietsch T, Gessi M, Rutkowski S, Bognar L, Klekner A, Cho BK, Kim SK, Wang KC, Eberhart CG, Fevre-Montange M, Fouladi M, French PJ, Kros M, Grajkowska WA, Gupta N, Weiss WA, Hauser P, Jabado N, Jouvet A, Jung S, Kumabe T, Lach B, Leonard JR, Rubin JB, Liau LM, Massimi L, Pollack IF, Shin Ra Y, Van Meir EG, Zitterbart K, Schuller U, Hill RM, Lindsey JC, Schwalbe EC, Bailey S, Ellison DW, Hawkins C, Malkin D, Clifford SC, Korshunov A, Pfister S, Taylor MD, Tabori U (2013) Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol 31(23):2927–2935. doi:10.1200/JCO.2012.48.5052