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MDB-63. AN INTERNATIONAL META-ANALYSIS OF SHH MEDULLOBLASTOMA SUBTYPES DEFINES A CLINICALLY SIGNIFICANT HIGH-RISK VARIANT OF SHH-SUBTYPE 3

Edward C Schwalbe[1,2], Martin Sill[3,4], Hiro Suzuki[5], Frederic Charron[6], Michael D Taylor[7,8], Stefan M Pfister[3,4], Steven C Clifford[1]; [1]Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle upon Tyne, United Kingdom, [2]Dept of Applied Sciences, Northumbria University, Newcastle upon Tyne, United Kingdom, [3]Hopp Children´s Cancer Center (KiTZ), Heidelberg, Germany, [4]German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany, [5]Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan, [6]Institut de Recherches Cliniques de Montréal (IRCM), Montréal, Canada, [7]The Arthur and Sonia Labatt Brain Tumor Research Centre, The Hospital for Sick Children, Toronto, Canada, [8]Baylor College of Medicine, Houston, USA

BACKGROUND: The distinction of MB_{SHH} into four methylation-dependent subgroups was recognized by the WHO in 2021. However, these subgroups have not previously been defined by international experimental consensus and their clinico-molecular features and behavior have not formally been investigated in large cohorts. We aimed to robustly identify SHH subgroups through analysis of MB_{SHH} with DNA-methylation profiling. METHODS: A cohort of 683 MB_{SHH}, confidently classified using the Heidelberg classifier v12.5, was assembled for analysis from multiple international studies. To define subgroups, we applied consensus sampling-based clustering approaches to tumor methylomes, including assessment of confidence in class-definition and inter-technique concordance. The clinico-molecular features of consensus subgroups were investigated. RESULTS: Lowest complexity analysis supported the division of MB_{SHH} into the 4 WHO-subtypes. SHH-1 and SHH-2 were associated with lower age and infrequent mutations of *PTCH1/SUFU*; SHH-2 was distinguished from SHH-1 by enriched MBEN histology, absence of chromosome 2 gain, less frequent metastasis and more favorable overall-survival. SHH-4 presented in older children and adults (3-57; median 24 years), and was primarily defined by mutations in *U1*-snRNA (67/72). Consensus analyses supported the division of SHH-subgroup-3 into three. Importantly, the SHH-3C subtype was associated with a coalescence of high-risk features (LCA histology, *TP53*mut, *MYCN*amp/*GLI2*amp) alongside 3p, 10q and 17p loss, and had dismal survival. The remaining SHH-3A/B subtypes were characterized by 9q loss, frequent focal amplifications of *TERT* and *PPM1D*, and equivalent better survival. CONCLUSIONS: This study affirms the distinction of MB_{SHH} into 4 major subgroups. For infant disease, SHH-2 is a favorable-risk marker. For childhood-MB_{SHH}, the SHH-3C subtype provides a molecular definition of high-risk that subsumes other previously-defined high-risk disease markers (LCA, *MYCN*amp, *TP53*mut) into a unified high-risk disease group. The other SHH-3 subtypes behave similarly and are favorable-risk. These subtypes have potential to enhance molecularly-guided risk-stratification in routine diagnostics, to improve patient outcomes and quality-of-life.