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# Transcriptome analysis stratifies second-generation non-WNT/non-SHH medulloblastoma subgroups into clinically tractable subtypes

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## Abstract

Medulloblastoma (MB), one of the most common malignant pediatric brain tumor, is a heterogenous disease comprised of four distinct molecular groups (WNT, SHH, Group 3, Group 4). Each of these groups can be further subdivided into second-generation MB (SGS MB) molecular subgroups, each with distinct genetic and clinical characteristics. For instance, non-WNT/non-SHH MB (Group 3/4) can be subdivided molecularly into eight distinct and clinically relevant tumor subgroups. A further molecular stratification/summarization of these SGS MB would allow for the assignment of patients to risk-associated treatment protocols. Here, we performed DNA- and RNA-based analysis of 574 non-WNT/non-SHH MB and analyzed the clinical significance of various molecular patterns within the entire cohort and the eight SGS MB, with the aim to develop an optimal risk stratification of these tumors. Multigene analysis disclosed several survival-associated genes highly specific for each molecular subgroup within this non-WNT/non-SHH MB cohort with minimal inter-subgroup overlap. These subgroup-specific and prognostically relevant genes were associated with pathways that could underlie SGS MB clinical-molecular diversity and tumor-driving mechanisms. By combining survival-associated genes within each SGS MB, distinct metagene sets being appropriate for their optimal risk stratification were identified. Defined subgroup-specific metagene sets were independent variables in the multivariate models generated for each SGS MB and their prognostic value was confirmed in a completely non-overlapping validation cohort of non-WNT/non-SHH MB (n = 377). In summary, the current results indicate that the integration of transcriptome data in risk stratification models may improve outcome prediction for each non-WNT/non-SHH SGS MB. Identified subgroup-specific gene expression signatures could be relevant for clinical implementation and survival-associated metagene sets could be adopted for further SGS MB risk stratification. Future studies should aim at validating the prognostic role of these transcriptome-based SGS MB subtypes in prospective clinical trials.

**Keywords:** Medulloblastoma; Non-WNT/non-SHH; Prognosis; Subgroups; Transcriptomic.

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