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The medulloblastoma methylome reveals new epigenetic regulatory mechanisms

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Much has recently been discovered with respect to genomic and transcriptomic alterations underlying medulloblastoma, the most common embryonal brain tumor. One of the most important insights is that medulloblastoma is not a single disease, but rather comprises four core molecular subgroups. We therefore sought to characterize global epigenetic alterations occurring in these medulloblastoma subgroups as part of the International Cancer Genome Project (ICGC) PedBrain Tumor project. In order to get a global, base-resolution profile of the medulloblastoma methylome, we performed high-coverage whole-genome bisulfite sequencing on 34 primary tumors and 8 normal cerebellum samples. To supplement this, we conducted genome-wide methylome analysis on >300 primary medulloblastomas (frozen and FFPE) using the Illumina Infinium HumanMethylation450 bead array. Matched transcriptome data from either microarrays or RNA sequencing, as well as miRNA sequencing data, was available for over 100 tumors, allowing us to correlate methylation with gene expression. DNA methylation was found to be correlated with overall expression levels and alternative isoforms in numerous regions. Interestingly, the strongest association was not at classical CpG islands, but downstream of transcription start sites. Differential methylation/expression between subgroups was observed for many known subgroup markers, but also novel candidiate genes (e.g. ARID1B, LIN28B) and miRNAs. Large-scale partially methylated domains (PMDs), identified in WNT and Group 3 tumors, were correlated with low gene expression and an increased somatic mutation rate. This study provides an extremely detailed view of the methylomic landscape of medulloblastoma, revealing novel insights into the epigenetic regulation of subgroup-specific mRNA and miRNA expression. Furthermore, the scope of the study has allowed us to identify associations between DNA methylation, gene expression, and alternative splicing / promoter usage which have wider implications for basic biology. These data will provide a basis both for future research studies and for the development of enhanced therapeutic modalities.