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The transcriptional landscape of medulloblastoma: Group 3 and 4 tumours comprise a single clinically significant expression continuum

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Transcriptome sequencing provides a far more precise and informative view of tumor biology than has hitherto been available. We sequenced the transcriptomes of 253 primary Medulloblastoma (MB) (~90M paired-end reads) with full clinical annotation, methylation and copy number profiles.

We find that MB may be defined as four transcriptional subgroups but the increased sensitivity of RNA-seq shows Group3 and Group4 MB tumors to exist along a dichotomous continuum of expression whereby tumors may exist as a series of intermediates. Moreover, this continuum is clinically significant; the more “Group3–like” an individual the greater the frequency of high-risk clinico-pathological/biological features and risk of death. Deriving a score to denote an individuals position along the continuum significantly outperforms the traditional four-subgroup model as a predictor of survival and reveals a strong correlation with MYC and MYC target expression.

By analysing the abundance of isoforms we were able to catalogue the predominant isoform expressed in MB and discover sub-group specific isoforms. De novo transcriptome assembly identifies several thousand previously undescribed transcripts/isoforms several hundred of which are sub-group specific with predicted coding potential. Fusion transcripts include predominantly PVT1 fusions and less frequently SUFU, MYCN. RNA single-nucleotide variants were also identified including subgroup specific RNA-editing events and allele specific expression. Several of these novel transcriptional events were selected for validation by qRT-PCR/Sequencing.

These findings raise important questions regarding the distinct nature of the Group3/Group4 subgroups particularly as they relate to risk stratification as well as providing a first highly detailed landscape of the MB transcriptome.