

ABSTRACT

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Unified rhombic lip origins of group 3 and group 4 medulloblastoma.

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Comment in

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Medulloblastoma, a malignant childhood cerebellar tumour, segregates molecularly into biologically distinct subgroups, suggesting that a personalized approach to therapy would be beneficial¹. Mouse modelling and cross-species genomics have provided increasing evidence of discrete, subgroup-specific developmental origins². However, the anatomical and cellular complexity of developing human tissues³-particularly within the rhombic lip germinal zone, which produces all glutamatergic neuronal lineages before internalization into the cerebellar nodulus-makes it difficult to validate previous inferences that were derived from studies in mice. Here we use multi-omics to resolve the origins of medulloblastoma subgroups in the developing human cerebellum. Molecular signatures encoded within a human rhombic-lip-derived lineage trajectory aligned with photoreceptor and unipolar brush cell expression profiles that are maintained in group 3 and group 4 medulloblastoma, suggesting a convergent basis. A systematic diagnostic-imaging review of a prospective institutional cohort localized the putative anatomical origins of group 3 and group 4 tumours to the nodulus. Our results connect the molecular and phenotypic features of clinically challenging medulloblastoma subgroups to their unified beginnings in the rhombic lip in the early stages of human development.

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