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Subtypes of medulloblastoma have distinct developmental origins

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Medulloblastoma encompasses a collection of clinically and molecularly diverse tumour subtypes that together comprise the most common malignant childhood brain tumour[1, 2, 3, 4]. These tumours are thought to arise within the cerebellum, with approximately 25% originating from granule neuron precursor cells (GNPCs) after aberrant activation of the Sonic Hedgehog pathway (hereafter, SHH subtype)[3, 4, 5, 6, 7, 8]. The pathological processes that drive heterogeneity among the other medulloblastoma subtypes are not known, hindering the development of much needed new therapies. Here we provide evidence that a discrete subtype of medulloblastoma that contains activating mutations in the WNT pathway effector *CTNNB1* (hereafter, WNT subtype)[1, 3, 4] arises outside the cerebellum from cells ofthe dorsal brainstem. We found that genes marking human WNT-subtype medulloblastomas are more frequently expressed in the lower rhombic lip (LRL) and embryonic dorsal brainstem than in the upper rhombic lip (URL) and developing cerebellum. Magnetic resonance imaging (MRI) and intra-operative reports showed that human WNT-subtype tumours infiltrate the dorsal brainstem, whereas SHH-subtype tumours are located within the cerebellar hemispheres. Activating mutations in *Ctnnb1* had little impact on progenitor cell populations in the cerebellum, but caused the abnormal accumulation of cells on the embryonic dorsal brainstem which included aberrantly proliferating Zic1$^+$ precursor cells. These lesions persisted in all mutant adult mice; moreover, in 15% of cases in which *Tp53* was concurrently deleted, they progressed to form medulloblastomas that recapitulated the anatomy and gene expression profiles of human WNT-subtype medulloblastoma. We provide the first evidence, to our knowledge, that subtypes of medulloblastoma have distinct cellular origins. Our data provide an explanation for the marked molecular and clinical differences between SHH- and WNT-subtype medulloblastomas and have profound implications for future research and treatment of this important childhood cancer.

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