SHH, G3 and G4), each of them further divided into subtypes with different prognosis and responses to therapy. Deregulation of chromatin modifier genes play an essential role in MB, particularly in the G4 subgroup. A $BMI1^{High}$;$CHD7^{Low}$ molecular signature identifies patients with poor survival. We have shown that $BMI1^{High}$;$CHD7^{Low}$ sustains MB growth through regulation of MAPK/ERK signalling and via epigenetic regulation of inositol metabolism in both G4 MB cells and patients. These tumours display overactivation of MAPK/ERK and AKT/mTOR pathways leading to energetic rewiring characterised by enhanced glycolytic capacity and reduced mitochondrial function. We demonstrate that inositol administration counteracts this metabolic alteration and significantly extends survival in an *in vivo* pre-clinical model. Additionally, we identify a synergistic vulnerability of G4 MB to a combination treatment with BMI1 and MAPK/ERK inhibitors that overcomes the acquired resistance induced by single drug therapies. Importantly, we have now analysed recurrent G4 MB and found that the $BMI1^{High}$;$CHD7^{Low}$ signature is maintained at recurrence and it continues to predict the pharmacological vulnerabilities we previously described. Finally, we extended the analysis to other paediatric brain tumours, including histone mutant gliomas and ependymomas, and identified molecularly defined subgroups that exhibit differential response to the compounds predicted to be effective by the $BMI1^{High}$;$CHD7^{Low}$ signature, hence expanding the spectrum of tumour potentially amenable to these novel pharmacological approaches.

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MDB-16. TARGETING EPIGENETIC DYSREGULATION IN PAEDIATRIC BRAIN TUMOURS
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Medulloblastoma (MB) is the most common paediatric malignant brain tumour and is classified into four distinct molecular subgroups (WNT,