findings in the mouse brain, EZHIP is not expressed at any time point or spatial location within the developing human brain. Taken together, these data reject the above hypothesis, that EZHIP or H3K27M co-opt an endogenous PRC2 inhibitory developmental program. Similarly, these results show that EZHIP is not expressed within the cell of origin for PFA or DMG. Further studies will seek to understand the endogenous function of EZHIP by further defining its normal expression pattern and function.

### TBIO-10. NGS MOLECULAR PROFILE OF PAEDIATRIC BRAIN TUMOURS: RESULTS FROM 92 CONSECUTIVE PATIENTS TREATED AT CENTRO HOSPITALAR UNIVERSITÁRIO DE SÃO JOÃO

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AIM: Our aim was to progress in bringing molecular medicine to routine clinical practice in the setting of paediatric neuro-oncology. We have implemented a protocol between Ipatimup and Centro Hospitalar Universitário de São João for the rapid and efficient delivery of the molecular portrait of paediatric brain tumours. MATERIAL AND METHODS: We have enrolled 92 patients with the following inclusion criteria: Age 0-18 years; newly diagnosed brain tumour; previously diagnosed brain tumour, whenever it presented as rare, aggressive or refractory disease; availability of tumour material; signed informed consent. Tumour samples were centrally reviewed by expert pathologists and profiled using the Oncomine Childhood Cancer Research Assay. RESULTS: In the 92 tumours that were molecularly profiled, *BRAF* was the most frequently altered gene, especially in pilocytic astrocytomas, being also detected in other LGG and HGG. Other commonly mutated genes were *PIK3CA* and *FGFR*, the former in HGG and the latter in LGG. *MYB* and *RAF1* rearrangements were also found in low grade glial/glioneuronal tumours, while HGG showed a more complex profile, with many cases harbouring multiple alterations in *EGFR, PDGFRA, ATRX, H3F3A, HIST1H3B, TP53*, among others. A 16-year old patient with CMMR (homozygous mutation in *PMS2*) developed a glioblastoma that carried nearly 5x the average number of mutations. Among the 8 medulloblastomas, 2 showed mutations in the SHH pathway (1 in *PTCH1* and one in *SUFU*) and 2 in the WNT pathway (1 in *CTNNB1* and one in *APC*). In the remaining cases, one ependymoma presented *MYCN* amplification, while no alterations were detected in 3 patients. CONCLUSIONS: This study enabled the detailed molecular study of 92 paediatric brain patients, allowing a more robust tumour classification and the identification of actionable alterations. A subset of the patients are already undergoing targeted therapy, mainly using BRAF or MEK inhibitors with generally good improvement.

### TBIO-11. THE GLUTAMINE TRANSPORTER AND CANDIDATE DIAGNOSTIC AND THERAPEUTIC TARGET SLC1A5 IS ASSOCIATED WITH SUBTYPE-SPECIFIC METABOLIC PHENOTYPES AND TUMOR PROGNOSIS IN PEDIATRIC BRAIN CANCERS

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Glutamine transporters play an important role in supporting increased tumor nutritional demands relative to non-cancerous cells, often through overexpression of the solute carrier (SLC) family of membrane transporters. Preclinical studies in adult cancers demonstrate that targeting glutamine addiction via SLC1A5 inhibition results in growth-inhibitory and tumoricidal effects. Given their relatively higher expression in cancer versus normal brain tissue, SLC transporters represent compelling targets for molecularly-targeted radiation and application of available prognostic amino-acid PET imaging probes. However, the role of SLC transporters in pediatric brain cancers has yet to be investigated. We aimed to understand the relationship of SLC transporter expression with pediatric brain tumor subtypes and their potential prognostic significance using data from the Pediatric Brain Tumor Atlas (PBTA). Using the expression of amino acid transporter genes in ensemble survival models (Reactome: R-HSA-352230), we found that elevated expression of glutamine transporters (SLC1A5, SLC7A5, SLC7A11, SLC38A5, SLC38A3) predicted shorter progression-free survival (PFS) in low-grade gliomas (LGGs) and poorer overall survival in pediatric ependymomas, high-grade gliomas (HGGs), and medulloblastomas. We focused specifically on SLC1A5 given the availability of imaging probes (18 F-Fluoroglutamine and 18F-Fluciclovine) for the corresponding amino acid transporter (ASCT2). Through transcriptome-based consensus clustering, we found that supratentorial, RELA fusion-positive ependymomas and sonic hedgehog-activated medulloblastomas were over-represented among clusters expressing higher levels of SLC1A5 ($p = 3.38e-7$ and $p = 2.18-26$, respectively). Kaplan-Meier analysis found that higher expression of SLC1A5 was associated with shorter OS in ependymoma and medulloblastoma ($p = 9.8e-4$ and $p = 0.032$) and shorter PFS in LGG ($p = 0.022$). Gene set analysis showed higher expression and network rewiring of amino acid, lipid, and immune pathways in SLC1A5-high expressing clusters. Our work demonstrates that glutamine transporters, particularly SLC1A5, represent compelling targets in pediatric brain cancers that warrant further investigation for molecularly-targeted treatment and amino-acid PET imaging.

### TBIO-12. SCREENING FOR CANCER PREDISPOSITION SYNDROMES IN PEDIATRIC NEURO-ONCOLOGY PATIENTS: A SINGLE INSTITUTION EXPERIENCE

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BACKGROUND: Traditional screening for cancer predisposition syndromes centers on family history, phenotypic features, and tumor histology. With expanded accessibility of next generation sequencing, identification of de novo germline mutations is increasing and the predictive value of family history has become less clear. While identification of germline mutations often affects care of pediatric neuro-oncology patients, germline sequencing is not currently standard of care. We hypothesize that routine screening for germline mutations in pediatric neuro-oncology patients reveals unsuspected cancer predisposition syndromes and impacts care. METHODS: A retrospective analysis was performed on pediatric neuro-oncology patients at a single institution who had targeted next generation sequencing of approximately 500-cancer associated genes (UCSF500) on tumor and paired germline DNA. We determined the proportion of patients with germline mutations and assessed impact on future screening and current tumor treatment. We interrogated clinical notes, family history, and interviewed treating physicians to determine if predispositions were previously suspected. RESULTS: Between June 2015-December 2019, 187 patients had paired testing; of these 29 (16%) harbored germlines mutations that were pathogenic or likely pathogenic. Germline mutations were found in patients with high-grade glioma (n=12), low-grade glioma (n=7), medulloblastoma (n=4), ATRT (n=2), and choroid plexus papilloma (n=1). Known cancer predisposition syndromes were identified or confirmed in 18 patients. Of these, the most common alterations were in TP53 (n=6), CHEK2 (2), NF1 (n=2), SMARCB1 (n=2), and PTEN (n=2). Patients were referred to genetic counseling in 26 cases and malignancy screenings were implemented in 25 cases. Germline findings affected malignancy treatment in 10 cases, most often through use of targeted therapeutics or avoidance of radiation. CONCLUSIONS: In our series, we found that 16% of pediatric neuro-oncology patients harbored germline mutations, the majority of which were associated with cancer predisposition syndromes. These results support standardizing screening for pathogenic germline mutations in pediatric neuro-oncology patients.

## VIRAL/GENE THERAPY AND OTHER NOVEL THERAPIES

### THER-01. PRECISION BRAIN TUMOR THERAPY BY AAV-MEDIATED ONCOGENE EDITING

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Pediatric high-grade glioma is a heterogeneous group of highly malignant tumors of the central nervous system, with a median overall survival of less than two years after diagnosis, demanding novel treatment options. One