(SNVs) in histones. However, the contribution of structural variants (SVs) to gliomagenesis has not been systematically explored due to limitations in early SV analysis approaches. Using SV algorithms, we recently created, we analyzed SVs in whole-genome sequences of 179 pHGGs including a novel cohort of treatment naïve samples–the largest WGS cohort assembled in adult or pediatric glioma. The most recurrent SVs targeted MYC isoforms and receptor tyrosine kinases, including a novel SV amplifying a MYC enhancer in the lncRNA CCDC26 in 12% of DMGs and revealing a more central role for MYC in these cancers than previously known. Applying de novo SV signature discovery, we identified five signatures including three (SVsig1-3) involving primarily simple SVs, and two (SVsig4-5) involving complex, clustered SVs. These SV signatures associated with genetic variants that differed from what was observed for SV signatures in other cancers, suggesting different links to underlying biology. Tumors with simple SV signatures were TP53 wild-type but were enriched with alterations in TP53 pathway members PPM1D and MDM4. Complex signatures were associated with direct aberrations in TP53, CDKN2A, and RB1 early in tumor evolution, and with extrachromosomal amplicons that likely occurred later. All pHGGs exhibited at least one simple SV signature but complex SV signatures were primarily restricted to subsets of H3.3K27M DMGs and hemispheric pHGGs. Importantly, DMGs with the complex SV signatures SVsig4-5 were associated with shorter overall survival independent of histone type and TP53 status. These data inform the role and impact of SVs in gliomagenesis and mechanisms that shape them.

HGG-61. LANDSCAPE OF CANCER PREDISPOSITION IN PEDIATRIC HIGH-GRADE GLIOMA

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Current estimates indicate that approximately 8–10% of cancer incidence in young patients can be attributed to constitutional alterations in genes linked to tumor initiation. The rarity and highly heterogeneous nature of high-grade glioma (HGG) in children and adolescents requires coordinated efforts to capture the diversity of subtypes in a normal-tumor matched sequencing cohort. Combining sequencing data of two registries based at the Hopp Children's Cancer Center (KiTZ) Heidelberg (INFORM and MNP2.0) allowed us to investigate the landscape of constitutional alterations across 350 children with high-grade gliomas. Both cohorts independently showed a surprisingly high proportion of patients (17%) with constitutional pathogenic alteration variants in cancer predisposition genes (n=40/233 and 23/128). Our results confirm a high frequency of alterations affecting genes of the DNA mismatch repair (MMR) pathway in 44% of IDH-mutant tumors (n=12/27). Additionally, we observed an almost exclusive correlation of MSH6 constitutional variation and somatic mutation in the IDH1 gene (n=7/8). A hypermutator phenotype defined by a tumor mutational burden >10 mutations/mb) was linked in 14/17 patients to a constitutional alteration in one of the following MMR genes: MLH1, MSH2, MSH6 or PMS2, with IDH-wildtype cases mostly classified as 'RTK1 subtype' by DNA methylation analysis. Constitutional alterations in TP53 were found in 5% of the total cohort. Furthermore, these tumors occurred exclusively in the group of H3-/IDH-wildtype glioblastoma (12%), and 8/18 tumors belong to the pedHGG_MYCN subgroup (conversely, this represents 40% of all 'MYCN subtype' patients, a highly significant enrichment over other subtypes (p<0.001). The overall high percentage of constitutional alterations in pediatric HGG warrants human genetics counselling for all affected patients and their families. Additionally, the strong correlation of MSH6 and IDH mutations as well as Li-Fraumeni-Syndrome and MYCN positive signature should be further explored as this might open the avenue for much needed new therapeutic approaches.

HGG-62. MOLECULARLY GUIDED TREATMENT OF MISMATCH REPAIR-DEFICIENT PEDIATRIC BRAIN TUMORS

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Mismatch repair (MMR)-deficient brain tumors, defined by high tumor mutational burden (TMB) and alterations in MMR or DNA proofreading genes, may harbor therapeutic vulnerabilities to immune checkpoint inhibition (ICI) and resistance to temozolomide. We report a single-institution experience incorporating a personalized genomics approach for pediatric brain tumor patients with high TMB. Tumor and peripheral blood samples were obtained at surgery or autopsy and molecular profiling performed by UWOncoPlex, a multiplexed DNA sequencing panel. Treatment and survival information was obtained by medical records review. Tumor types included high-grade glioma (10, including 1 DIPG), and desmoplastic/nodular medulloblastoma (1). Metachronous tumors were present in three patients and median age at diagnosis was 11.5 years (range 8 – 18). Constitutional predisposition included MMR deficiency (CMMRD), Lynch syndrome, and polymerase proofreading deficiency (PPD). All patients had localized disease, with gross total resection achieved in 6/11 (55%). All received radiation (RT), with concurrent temozolomide delivered in HGG (9). 7/9 patients (78%) with HGG had radiographic progression following RT/temozolomide. Five patients received ICI with pembrolizumab (4), nivolumab/ipilimumab (2), or nivolumab alone (1). Two patients progressed on pembrolizumab then had partial responses to dual nivolumab/ipilimumab. Another patient had a complete response to pembrolizumab and remains disease-free nearly 1 year after discontinuing drug due to reactivated skin GHVD. While not statistically significant in this small cohort, median survival of ICI-treated patients (5) compared to those who received alternative therapies (6) was 40.4 vs. 17.7 months. Patients with durable responses >18 months to ICI (3) included one who underwent surgical debulking following nivolumab, and two patients molecularly classified as CMMRD + somatic PPD. This series highlights the importance of integrating molecular findings and identification of high TMB early in clinical diagnosis and supports the use of ICI to achieve durable responses in children with MMR-deficient brain tumors.

IMAGING

IMG-01. QUANTITATIVE DIRECT SODIUM (23NA) MRI IN PEDIATRIC GLIOMAS

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BACKGROUND: The treatment of pediatric gliomas is typically assessed with proton (^{1}H) MRI, which can have limitations. ^{23}Na MRI has been shown in adult brain tumors to measure intra-tumoral total sodium concentration as a correlate of tumor proliferation. ^{23}Na MRI sodium studies in pediatric patients are lacking. PURPOSE: (1) To compare total sodium concentration (TSC) between pediatric glioma and non-neoplastic brain tissue using ^{23}Na MRI; (2) Compare tissue conspicuity of bound sodium concentration (BSC) using ^{23}Na MRI dual echo relative to TSC imaging. MATERIALS AND METHODS: TSC was measured in: (1) non-neoplastic brain tissues and (2) three types of manually segmented gliomas [diffuse intrinsic brainstem glioma (DIPG), recurrent supratentorial low-grade glioma (LGG), and high-grade glioma (HGG)] on sodium MRI images co-registered with proton MRI. In a subset of patients, serial changes in both TSC and BSC (dual echo ^{23}Na MRI) were assessed for tissue conspicuity using voxel-based parametric maps. RESULTS: Twenty-six pediatric patients with gliomas (median age of 12.0 years, range 4.9 – 23.3 years) were scanned with ^{23}Na MRI. Uninvolved tissues demonstrated a range of TSC values similar to published adult values. DIPG treated with RT demonstrated higher TSC values than the uninvolved infratentorial tissues (P<0.001). Recurrent supratentorial LGG and HGG exhibited higher TSC values than the uninvolved white matter (WM) and gray matter (GM) (P<0.002 for LGG, and P<0.02 for HGG). The dual echo ^{23}Na MRI suppresses the sodium signal within both CSF and necrotic foci, resulting in improved conspicuity of both non-neoplastic and neoplastic, compared to serial TSC imaging. CONCLUSION: Quantitative ^{23}Na MRI of pediatric gliomas demonstrates a range of values that are higher than non-neoplastic tissues. Dual echo ^{23}Na MRI of BCS improves tissue conspicuity relative to TSC imaging. Future studies are needed to determine the value of ^{23}Na MRI in delineating therapeutic responses in pediatric gliomas.

IMG-02. IMPROVED PREDICTION OF POSTOPERATIVE PAEDIATRIC CEREBELLAR MUTISM SYNDROME USING AN ARTIFICIAL NEURAL NETWORK

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