fusions and p53 protein showed characteristic cytoplasmic positivity; Patient3 presented a brand-new ALK-QKI fusion combined with ALK mutation and focal SMARCB1 deletion. All these 3 cases received corresponding targeted therapy, acquiring a good response to the normal treatment. In the present study, the role of TPD52 IHC in medulloblastoma still needs further research. METHOD: Immunohistochemistry, fluorescent in situ hybridization and whole-transcriptome sequencing. RESULTS: Case 18 months, male, right hemisphere center occupation. Histopathology: High-grade neuroepithelial neoplasm. IHC: GABA(B)R2(-), Olig2(+), Vimentin(+), P53(cytoplasm)+, pan-TRK-(+), Ki67(25%+). Reticular fiber staining showed biphasic tissue pattern with reticulin-rich sarcomatous and reticulin-free gliomatous elements. Characteristic Molecular Information: NTRK1-TPD52 fusion. Follow-up: 14 months, alive. CONCLUSION: Infant-type hemispheric glioma is a special kind of glioma, which is particularly suitable for precision medicine treatment approaches. Their overall survival is good compared with other three pHGG subtypes.

PATH-02. USING DNA METHYLATION PROFILING TO DEFINE TUMOR TYPE AND APPROPRIATE TREATMENT: A CASE REPORT AND REVIEW OF THE LITERATURE OF A RARE CNS CIC ALTERED SARCOMA
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The utilization of methylation profiling is increasingly becoming part of the standard evaluation for high-grade malignancies. CNS primary tumors with CIC alteration are a recently recognized CNS tumor entity identified via DNA methylation profiling of primitive neuroectodermal tumors (PNET). PNETs have historically carried a poor overall prognosis; however, CNS tumors with CIC alteration have rarely been described in the past. The tumor which remains to be discussed regarding the presentation, tumor characteristics, outcomes, and ideal treatment strategy to optimize survival in these patients. We describe the case of a 2-year-old Hispanic female with a CNS primary tumor with CIC alteration. This patient initially presented with a five-week history of fatigue, headaches, enuresis, and right-sided muscle weakness and was found to have a right-sided supratentorial mixed solid and cystic mass. The initial diagnosis was consistent with a high-grade neuro-epithelial tumor based on histology and standard CNS tumor genetic markers. Due to poorly defined tumor characteristics, a sample was also sent for DNA methylation profiling. The profiling pattern was consistent with a CNS CIC altered sarcoma thereby significantly altering the treatment plan. Accurate diagnosis is critical in managing patients with cancer. DNA methylation profiling has contributed to diagnostic accuracy in these aggressive tumors; however, it creates challenges with beginning treatment expeditiously due to the time required for processing and interpretation. This case illustrates the positive utility of DNA methylation to better characterize tumor types and the impact this has on both treatment as well as prognosis.

PATH-03. CLINICALLY TRAJECTORY OBTAINABLE PREDICTION OF GROUP 3/4 MEDULLOBLASTOMA BASED ON TPD52
IMMUNOHISTOCHEMISTRY: A MULTICOHORT STUDY
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BACKGROUND: International consensus and the 2021 WHO classification of CNS tumors recognize eight molecular subgroups among Group 3/4 medulloblastoma (HRs between 3.67-26.7 [95% CIs between 1.00-706.23], p = 0.05, 0.017 and 0.0058). Cross-validated survival models incorporating TPD52 IHC with clinical and molecular features (subgroup affiliation, MYC status) outperform existing gene-expression based risk stratification schemes in terms of prediction error, area under the ROC curve and C-statistic. RESULTS: TPD52 IHC, percentage positivity represents a significant independent predictor of early relapse and survival. A median TPD52 bioinformatically validated across three Group 3/4 medulloblastoma clinical cohorts (n = 387) treated with conventional therapies. Risk stratification and prediction capability were computed utilizing uni- and multivariate survival analysis. Newly developed risk classifiers including TPD52 IHC were compared to state-of-the-art risk stratification schemes in terms of prediction error, area under the time-dependent receiver operating characteristic (ROC) curves and C-statistic. RESULTS: TPD52 IHC, percentage positivity represents a significant independent predictor of early relapse and survival. A median TPD52 bioinformatically validated across three Group 3/4 medulloblastoma clinical cohorts (n = 387) treated with conventional therapies. Risk stratification and prediction capability were computed utilizing uni- and multivariate survival analysis. Newly developed risk classifiers including TPD52 IHC were compared to state-of-the-art risk stratification schemes in terms of prediction error, area under the time-dependent receiver operating characteristic (ROC) curves and C-statistic. RESULTS: TPD52 IHC, percentage positivity represents a significant independent predictor of early relapse and survival. A median TPD2 bioinformatically validated across three Group 3/4 medulloblastoma clinical cohorts (n = 387) treated with conventional therapies. Risk stratification and prediction capability were computed utilizing uni- and multivariate survival analysis. Newly developed risk classifiers including TPD52 IHC were compared to state-of-the-art risk stratification schemes in terms of prediction error, area under the time-dependent receiver operating characteristic (ROC) curves and C-statistic. RESULTS: TPD52 IHC, percentage positivity represents a significant independent predictor of early relapse and survival. A median TPD2 bioinformatically validated across three Group 3/4 medulloblastoma clinical cohorts (n = 387) treated with conventional therapies. Risk stratification and prediction capability were computed utilizing uni- and multivariate survival analysis. 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The classification of human brain tumors by global DNA methylation profiling has become an essential part of modern integrated neuropathological diagnostics. It has proven to reliably identify known and novel brain tumor (sub-)types that are biologically and clinically distinct. Therefore, this technique is widely applied, especially in high-volume centers, for improved diagnostic accuracy and risk stratification of brain tumor patients. Although indispensable for the understanding of tumor biology and for preclinical drug trials, the comparison of genetically engineered mouse models to human brain tumors is still difficult. The assessment of tumor morphology only provides an approximate picture, and transcriptomic data from human brain tumors are sparse and suffer from platform-related technical incomparability. Here, we show array-based DNA methylation profiling of well-established murine brain tumors, such as Wnt and Shh medulloblastoma, YAP and RELA ependymoma, ETMR, and AT/RT. Similar to human brain tumors, unbiased clustering methods revealed distinct methylation profiles and mean methylation levels for mouse brain tumor types. Analyses were possible for fresh-frozen as well as for paraffin-embedded tissue, and copy number alterations could be inferred from methylation profiles. Most importantly, results suggest that interspecies comparisons allow the classification of brain tumors from known or novel mouse models based on the constantly growing spectrum of human brain tumor types and subtypes with hundreds of thousands of available disease samples. As an example, upon DNA methylation profiling, cerebellar tumors arising in Matf8cre;SmoM2fl/+ mice display the highest similarity to human SHH medulloblastoma when compared to multiple human brain tumor entities including WNT and Non-WNT/Non-SHH medulloblastoma. This pilot study suggests that global DNA methylation profiling may add another very important level of information to the characterization of genetically engineered mouse models.

PATH-05 CHALLENGE AND CLINICAL RELEVANCE OF A NON-MATCHING CLASSIFIER OUTPUT IN GENOME-WIDE DNA METHYLATION ANALYSIS FOR CNS NEOPLASMS IN PEDIATRIC AND ADULT PATIENTS

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OBJECTIVE: The molecular classification of CNS tumors has revolutionized our understanding of the biological heterogeneity and diversity of tumor subtypes. DNA methylation-based classification allows to discriminate subtypes. Although DNA methylation-based classification can diagnose tumors with high specificity, there are tumors which cannot be classified. We aimed to gain further insight into these challenging cases. METHODS: Overall, 21 patients with a CNS tumor that was non-classifiable by using the DNA methylation score <0.3, or a DNA methylation classifier version 11.4 using the DNA methylation-based classifier version 11b4, were included. Tumors were re-classified using version v12.3, and clinical data were analyzed. RESULTS: A total of 21 pediatric and adolescent brain tumors with a calibrated score below 0.7 in the treatment of pilocytic astrocytoma, and 10 cases were pilocytic astrocytomas. Of these, 11 patients (52.4 %) were assigned to the “no matching methylation class” with a score below 0.3. IDH-wild type glioblastoma (23.8 %), non-IDH-mutated glioblastoma (21.4 %) and AT/RT. Similar to human brain tumors, unbiased clustering methods and transcriptomic data from human brain tumors are sparse and suffer from high economic cost and sample input requirements. Currently, no optimised pipeline exists that is tailored to handle samples sequenced at low-pass (i.e., <10x depth). METHODOLOGY: Two datasets were utilised; 36 newly sequenced low-depth (10x) were applied for WGBS, the 10x WGBS dataset achieved 96% sensitivity compared to microarray approaches. A pilot study of the suitability of FFPE was promising, and we demonstrate that WGBS data can be integrated into existing array-trained models with high assignment probabilities. Also, WGBS-derived classifier performance measures exceeded microarray-classified-derived classifiers. CONCLUSION: We describe a platform-independent WGBS assay for molecular subgrouping of murine glioma to reliably analyze its correlation, at an increasingly comparable cost ($400 vs $80) and provides a proof-of-concept for routine clinical application using standard WGS technology. Finally, the full methylene enabled elucidation of additional biological heterogeneity that has hitherto been inaccessible.

PATH-07. DIAGNOSTIC AND THERAPEUTIC VALUE OF CEREBROSPINAL FLUID BIOSPY IN PEDIATRIC BRAIN TUMORS

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BACKGROUND: The application of cerebrospinal fluid (CSF) biopsy in brain tumors is valuable. This paper further explores the diagnostic and therapeutic value of CSF biopsy in pediatric brain tumors. METHODS: In this study, children with primary brain tumor aged ≤18 years old in Guangdong Sanjiu Brain Hospital were enrolled if NGS testing was required for all included patients. The genetic mutations in these children were analyzed. RESULTS: A total of 12 pediatric brain tumors who underwent CSF NGs were included in this study. 9 patients were brainstem glioma and 3 were pilocytic astrocytoma. The mutated genes were detected in 67% (8/12) patients by CSF NGs. In brainstem glioma, the rate was 67% (6/9), and the most common genes were H3F3A (5/6, 83%) and TP53 (5/6, 83%). Other detected genes included EGF, CDK4 and NFI. H3F3A mutation is of great significance for the diagnosis of brainstem glioma, and EGF is valuable for the treatment. In pilocytic astrocytoma, the detection rate was 67% (2/3), and the genes included KIAA1549-BRAF fusion, FGFR1 and PTEN11 mutations. KIAA1549-BRAF fusion is of great value in the diagnosis of adult or juvenile pilocytic astrocytoma, and FGFR is valuable in the treatment. CONCLUSIONS: Fluid biopsy of CSF for pediatric brain tumors may be an important supplement to histological diagnosis, especially when histopathology is not available. The results are significant for the diagnosis and treatment of pediatric brain tumors.

PATH-08. DNA METHYLATION PROFILING IMPROVES ROUTINE DIAGNOSTICS OF PAEDIATRIC CNS TUMOURS: A PROSPECTIVE POPULATION-BASED STUDY

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