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Diffuse leptomeningeal glioneuronal tumors (DLGNT) are rare neoplasms of the central nervous system. We describe the generation of patient-derived models from a DLGNT that metastasized to the peritoneal cavity via a ventriculoperitoneal shunt in a child. The original tumor contained a KIAA1549:BRAF fusion with a chromosome 1p deletion and corresponded with methylation subclass DLGNT-MC-2 From a sample of ascitic fluid, metastatic tumoral cells could be extracted and expanded ex vivo into a long-term cell culture model. This patient-derived cell line (PDCL) showed mixed morphological phenotypes and expressed MAP2 and SYP. The KIAA1549:BRAF fusion was preserved and the PDCL still corresponded to the original methylation subclass DLGNT-MC-2. Whole-genome sequencing showed additional mutations potentially contributing to the malignant behavior of the tumor. Cytotoxic assays performed on the PDCL indicated high sensitivity to vinblastine and trametinib (MEK-inhibitor) and intermediate sensitivity to DRD/ClpP-modulators. The PDCL underwent viral transduction to induce GFP-fLux positivity and was intraperitoneally injected into immunocompromised mice. A mouse model could be generated, with the growth of a peritoneal tumor in a localized manner. The cells grown from the mouse tumor were again put into culture and were afterwards subjected to the same treatments as the PDCL. This confirmed a similar profile, with high sensitivity to vinblastin and trametinib and an intermediate sensitivity to the DRD/ClpP-modulators. In conclusion, we were able to generate patient-derived models from a metastatic DLGNT, which recapitulate the molecular characteristics of the original tumor. The models showed high sensitivity to vinblastin and targeted therapy with MEK-inhibition, but further studies are necessary to define the adequate treatment for this kind of tumor.

OTHR-40. DICER 1- A RARE , BUT IMPORTANT TUMOR DRIVER IN MALIGNANT PROGRESSIVE BRAIN TUMORS

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BACKGROUND: DICER mutation is a known tumor driver involved in pleuropulmonary blastoma ,renal tumors, masses in the thyroid and ovary and multiple other manifestations. Brain tumors are considered to be a rare manifestation of germline DICER mutation. Currently, brain imaging is not included in the standard follow up of patients with DICER germline mutation, and data re the prevalence of somatic DICER mutations in brain tumors is limited. AIMs: evaluation of prevalence of DICER mutations in a large cohort of rare/relapsed brain tumors. METHODS: over the last year all patients with tumors lacking curative standard therapy in Israel were sent for next generation sequencing,. Molecular evaluation was done using either panel based evaluation (ONCOMINE/ Foundation) or whole exome and whole transcriptome (INFORM consortium). Epidemiological data as well as clinical outcome were provided by the treating physician. RESULTS: Between April 2021 and January 2022 one hundred twenty nine samples were sent for molecular analysis, 58 of them were brain tumors. Six patients had DICER associated malignant tumors , 33% of them were brain tumors . One patient with pinealoblastoma was diagnosed with a highly metastatic disease associated with a very grave prognosis. CONCLUSION: brain tumors are an important group among malignant DICER associated tumors. Surveillance may lead to early detection which may be associated with a better outcome.

OTHR-41. AMPLIFICATION OF THE PLAG FAMILY GENES – PLAGL1 AND PLAGL2 – IS A KEY FEATURE OF A NOVEL EMBRYONAL CNS TUMOR TYPE

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Pediatric central nervous system (CNS) tumors differ substantially from their adult counterparts, are marked by considerable molecular and clinical heterogeneity, and diagnosis through histopathology alone can be challenging. Using DNA methylation-based CNS tumor classification in combination with copy number and RNAseq analysis, we identify a rare, novel pediatric CNS tumor type (n=32) which is characterized by focal high-level amplification and consecutive overexpression of one of the PLAG family genes – PLAGL1 or PLAGL2. It is epigenetically divergent from other known tumor types such as high-grade gliomas, medulloblastomas, embryonal tumors, or CNS sarcomas. The wide range of original histopathologic diagnosis rendered attests to their polyphenotypic nature in terms of morphology. We suggest that these tumors may arise from early to intermediate neural progenitor cells with some neuronal commitment. Using ChIPseq data, we show that both PLAGL1 and PLAGL2 act as transcription factors for: i) the oncogenic kinase RET, a potential drug target, that was overexpressed in our cohort; ii) components of the Wnt/β-Catenin pathway; iii) a set of imprinted genes, reported to regulate the imprinted gene network in mouse models, that was deregulated in the PLAGL-amplified tumors. Consequently, a 250-gene expression PLAGL-signature indicated dysregulation of imprinting control and differentiation/development as a prominent feature. We report differences regarding age and sex distribution between PLAGL1- and PLAGL2-amplified tumors and shed light on differences in clinical behavior and outcomes between these subtypes in male and female patients. PLAGL1-amplified tumors were more prevalent in school-age children and teenagers, while PLAGL2-amplified cases occurred in very young patients. Kaplan-Meier analysis showed a trend towards a more favorable outcome in patients with PLAGL1-amplified tumors and in female patients. Survival rates remained constant after 5 years with a five-/ten-year overall survival of 75% for PLAGL1, 24% for PLAGL2, 18% for male patients, and 88% for female patients.

OTHR-42. MISSING DATA TOLERANT INTEGRATION OF PROTEOMIC DATASETS ENABLES THE IDENTIFICATION AND CHARACTERIZATION OF BRAIN CANCER SUBTYPES

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Investigating the proteome can add a significant layer of information to manifold existing methylation, mutation, and transcriptome data on brain tumors as proteins represent the pharmacologically addressable phenotype of a disease. Small cohorts limit the usability and validity of statistical methods, and variable technical setups and high numbers of missing values make data integration from public sources challenging. Using a newly developed framework being able to reduce batch effects without the need for data reduction or missing value imputation, we show –based on in-house and publicly available datasets- successful integration of proteomic data across different tissue types, quantification platforms, and technical setups. Exemplarily, data of a Sonic hedgehog (Shh) medulloblastoma mouse model were analyzed, showing efficient data integration independent of tissue preservation strategy or batch. We further integrated batches of publicly available data of human brain tumors, confirming proposed proteomic cancer subtypes correlating with clinical features. We show that, missing value tolerant reduction of technical variances may be helpful to identify biomarkers, proteomic signatures, and altered pathways characteristic for molecular brain cancer subtypes.