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BACKGROUND: Cell-free DNA (cfDNA) profiling has been shown to carry utility as a clinically relevant biomarker in a variety of cancers, but studies in pediatric brain tumors, including medulloblastoma, are scarce. We hereby evaluated the actionability of profiling cfDNA from cerebrospinal fluid (CSF) based on a multi-institutional cohort of children with medulloblastoma. METHODS: 103 children aged ≥ 3 years with medulloblastoma harboring chromosomal aneuploidy enrolled on two prospective therapeutic trials were included. cfDNA was extracted from CSF obtained longitudinally, and profiled by low-coverage whole-genome sequencing (lcWGS) for annotating copy-number variants (CNVs). cfDNA-derived CNVs were compared against patient-matched primary tumor-derived CNVs and correlated with outcome. cfDNA profiles at diagnosis and relapse were compared to evaluate tumor evolution. RESULTS: Tumor-derived somatic CNVs were detected in 72% of baseline cfDNA samples, with higher detection rate in samples from patients with metastatic disease than those without (90% versus 50%, chi-square p=0.001). Longitudinal profiling of cfDNA revealed correlation between CNV detectability and clinical course, with detection of tumor-derived CNVs in cfDNA samples predating radiographic progression for ≥ 3 months in 62% of relapsing patients. Presence of cfDNA-derived CNVs in CSF collected during chemotherapy and at the end of therapy was significantly associated with inferior PFS (log-rank p<0.0001 for both time-points). Comparison of CNV profiles from cfDNA at baseline and relapse revealed molecular divergence in a subset of patients. CONCLUSION: These results carry major implications and supports the incorporation of cfDNA profiling in upcoming medulloblastoma protocols for more sensitive and accurate disease monitoring and personalization of treatment.

MBRS-21. CLINICAL AGGRESSIVENESS OF TP53-WILD TYPE SONIC HEDGEHOG MEDULLOBLASTOMA WITH MYCN AMPLIFICATION

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Clinical implication of MYCN amplification in sonic hedgehog (SHH) medulloblastoma may still be controversial due to the frequent co-occurrence with TP53 mutation, which is one of the poorest prognostic factors among the subgroup. We described two cases of TP53-wild type SHH medulloblastoma with MYCN amplification, showing dismal clinical course with rapid disseminated relapse just after the end of treatment. CASE 1: A 7-year-old boy developed a non-metastatic cerebellar tumor. Pathology of the tumor was consistent with classic medulloblastoma. The patient received treatment that involved reduced-dose (18 Gy) craniospinal irradiation (CSI), local irradiation, and chemotherapy. However, sudden respiratory arrest developed due to massive intracranial disseminated relapse 9 months after the initial surgery. CASE 2: A 6-year-old boy presented a large mass in his 4th ventricle without dissemination. He diagnosed with large cell/anaplastic medulloblastoma and underwent radiation therapy (24 Gy of CSI and local irradiation) and chemotherapy, followed by high-dose chemotherapy. However, dissemination through neuroaxis occurred 9 months after the diagnosis. Methylation data of the cases was entered into a recently published classifier and both tumors were classified as "medulloblastoma, subclass SHH A (children and adult)". Copy number analysis demonstrated MYCN amplification in both cases. TP53 mutation analysis from exon 2 to 10 indicated wild type in one case. Additionally, p53 immunochemistry in both cases also indicated wild type. The cases remind us of the clinical aggressiveness of SHH medulloblastoma with MYCN amplification, even if there is no TP53 mutation. The tumor should still be treated with the most intensified treatment.

MBRS-22. SIGNIFICANCE OF *RNF213* IN TUMORGENICITY OF MEDULLOBLASTOMA

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RNF213 gene, initially identified as a disease-causing gene for moyamoya cerebrovascular disease, has recently been recognized as a tumor regulator. The gene is known to be associated with WNT signaling, lipid metabolism, angiogenesis and genomic instability. The purpose of this study was to investigate the association of *RNF213* in tumorgenicity of medulloblastoma. Incidence of medulloblastoma and histopathological findings were compared among *ptch1*+/-, *ptch1*+/- *rnf213*+/-, and *ptch1*+/- rnf213-/- mice. Knockout of *rnf213* in *ptch1*+/- transgenic mouse model increased the incidence of spontaneous generation of medulloblastoma from 19.8% (*ptch1*+/-) to 76.5% (*rnf213*+/- *ptch1*+/-) at 9 months ($p < 0.001$). Heterozygous knockout was equivalent to homozygous knockout. Haploinsufficiency of *rnf213* seems to be associated with tumorgenicity in medulloblastoma. Molecular mechanism of medulloblastoma generation needs to be further investigated.

MBRS-23. SIGNIFICANCE OF MI-R33 IN GENERATION AND PROGRESSION OF MEDULLOBLASTOMA

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Lipid metabolism has been shown to be associated with tumorigenicity in various malignancies. The purpose of this study was to investigate the association of miR-33, a key regulator of lipid metabolism, in tumorigenicity and progression of medulloblastoma. miR-33a is an only isotype of miR-33 in rodents although miR-33b is also detected in human. Incidence of medulloblastoma and histopathological findings were compared between ptch1+/- mice and ptch1+/- miR-33a-/- mice. Effect of miR-33b upregulation by cordycepin was tested in DAOY medulloblastoma cells both in vitro and in vivo. Knockout of miR-33a in ptch1+/- transgenic mouse model increased the incidence of spontaneous generation of medulloblastoma from 19.8% to 49.5% ($p < 0.001$) at 10 months. Cordycepin, which upregulates miR-33b, prevented tumor growth in DAOY human medulloblastoma cell line, but the effect was not evident in an orthotopic mouse medulloblastoma model. Although miR-33 seems to be an important regulator of medulloblastoma, treatment efficacy of cordycepin was not enough. Combination treatment with immunotherapy or cytotoxic treatment needs to be tested to show survival benefit in preclinical models.

MBRS-24. FUNCTIONAL CHARACTERIZATION OF IKBKAP/ELP1 AS A NOVEL SHH MEDULLOBLASTOMA PREDISPOSITION GENE

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Medulloblastoma (MB), a common malignant pediatric brain tumor, comprises at least four distinct molecular entities: WNT, SHH, Group 3, and Group 4. SHH-MB is driven by aberrant activation of the Sonic hedgehog (SHH) pathway in granule neuron progenitors (GNPs) and is associated with hereditary cancer predisposition syndromes including Li Fraumeni and Gorlin. We recently identified germline loss of function (LoF) mutations affecting *IKBKAP/ELP1*, the primary scaffolding subunit of the Elongator complex in a subset of SHH-MB patients. Germline *ELP1* mutations account for ~15% of all pediatric SHH-MBs and position *ELP1* as the most prevalent hereditary predisposition gene in MB. We genetically engineered *Elp1* LoF in mouse GNPs to determine Elp1 function in cerebellar development and SHH-MB. Results of both mechanistic and phenotypic experiments demonstrate that GNPs harboring *Elp1* loss exhibit ribosome pausing and protein aggregation, reinforcing the critical role of Elp1 in translational elongation and protein homeostasis. Further, we generated new transgenic mouse models mimicking germline *ELP1* LoF mutations observed in SHH-MB patients. *Elp1*+/- transgenic mice exhibit purkinje cell