

results revealed that NF2 mutations were the most common (5). Other meningioma related genes with mutations identified in our patient cohort include TRAF7, AKT3, MSH4 (2), KMT2C (2), TET1 (2), KDM6A, and MLH3. Copy number alterations were noted with increased frequency on chromosomes 1p, 22q, 19q. 850k methylation analysis did not conclusively show any clustering. Ongoing studies include assessment of tumor mutation burden, RNAseq, and the mutational profile. Conclusions: This study examined RIM in patients who received similar doses of radiation for their childhood cancer. To date, our findings are consistent with previously described primary and RIM mutations. Enhanced knowledge in secondary meningiomas is crucial for accurate patient counseling, prognostication, and treatment.

#### RARE-16. A PATIENT WITH MOSAIC POST-ZYGOTIC KRAS-G12D PATHOGENIC VARIANT PRESENTING WITH A SYMPTOMATIC SPINAL NEUROFIBROMA AND LARGE SEGMENTAL TRUNCAL CAFÉ AU LAIT SPOT

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An 11 year old boy presented with a three month history of progressive bilateral lower extremity weakness associated with recent intermittent incontinence. Spine MRI showed a right-sided T11-T12 paraspinous mass extending through the neural foramina into the epidural space and causing severe spinal cord compression. Skin showed a large macular lightly-hyperpigmented café au lait spot with irregular borders along the T10-T12 dermatome extending from the spine to approximately the anterior-axillary line. He was suspected to have segmental neurofibromatosis type 1 (NF1) as no additional clinical findings, radiographic features or family history of NF1 were identified. Patient underwent T10-12 laminectomy for resection of the epidural tumor component. Post-operative MRI showed resolution of the mass effect on the thecal sac and cord, with expected tumor residual lateral to the neural foramen. His residual spinal tumor and mild scoliosis remained stable over the two years of follow up to date. Pathological and molecular analysis of the resected tumor revealed a neurofibroma harboring an activating KRAS c.35G>A, p.Gly12Asp (KRAS-G12D) pathogenic variant at 27% variant allele frequency. Melanocytes cultured from two hyperpigmented skin biopsies showed the same KRAS-G12D pathogenic variant. This KRAS-G12D pathogenic variant was not found in leukocytes, indicating a post-zygotic origin. No NF1 pathogenic variant was identified in tumor tissue, melanocytes or leukocytes. The clinical findings were consistent with a mosaic KRASopathy due to a post zygotic KRAS-G12D pathogenic variant. The presence of the KRAS variant in the spinal neurofibroma and overlying café au lait spot without an NF1 etiology in associated tissues demonstrates overlapping variability of presentations of RAS-MAPK pathway disorders. This case highlights the need for full clinical and genetic evaluation of patients presenting with segmental neurocutaneous disorders.

#### RARE-17. HIGH-THROUGHPUT SCREEN IDENTIFIES POTENTIAL CHEMOTHERAPIES FOR CHOROID PLEXUS CARCINOMA TREATMENT USING INTRAARTERIAL STRATEGY

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Choroid plexus carcinoma is a rare infantile brain tumor with an aggressive clinical course.<sup>1</sup> There is no optimal treatment and survival is poor. Gross total surgical removal is the single most important predictor of survival.<sup>1</sup> Gross total surgical removal rates are inconsistent and associated with significant morbidity owing to the hemorrhagic nature of these tumors compounded by a small circulating blood volume. Neoadjuvant systemic chemotherapy with “second look surgery” helps to achieve gross total surgical removal<sup>2</sup> but has an inefficient pharmacokinetic profile and exposes children to dose-limiting toxic side effects. Hence, there is a strong need to identify and develop new agents and strategies to improve current choroid plexus carcinoma (CPC) treatment. Here, we report a high-throughput drug screening using a CPC cancer tissue-originated from a 7-year-old male patient and procured (Children's Cancer Hospital Egypt) to identify new potent drugs. The selected candidates have been used as single agent and combination agent chemotherapy to propose a relevant study (e.g. pharmacokinetics, toxicity, biodistribution, anticancer efficacy) for improving CPC treatment using a pre-existing intraarterial chemotherapy. A genetically engineered model has been developed by Shannon et al by breeding RosamTmG with Nestin-Cre to generate *Nestin-cre/RosamTmG* reporter mice overexpressing c-Myc, which provides a fully penetrant model of CPC in the lateral ventricle CP and 4<sup>th</sup> ventricle CP.<sup>3</sup> This mice model will be used to explore *in vivo* the newly discovered drug combinations to treat the CPC tumor. 1. Hosmann, A. et al. Management of choroid plexus tumors—an institutional experience. *Acta Neurochir. (Wien)*. 161, 745–754 (2019) 2. Schneider, C. et al. Neoadjuvant chemotherapy reduces blood loss during the resection of pediatric choroid plexus carcinomas \*christian.

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#### RARE-18. NF1-MUTATED TUMORS EXHIBIT INCREASED SENSITIVITY TO AUTOPHAGY INHIBITION ALONE AND IN COMBINATION WITH MEK INHIBITION

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Background: Autophagy inhibition is a potential treatment for central nervous system (CNS) tumors. Autophagy, a heavily regulated process by which cellular waste is transferred to lysosomes for degradation and processing, is an integral part of tumor cell survival under stressful conditions including nutrient deprivation and chemotherapy. While the efficacy of autophagy inhibition has been demonstrated in CNS tumors with BRAF<sup>V600E</sup> mutations, it has yet to be explored in other CNS tumor types with MAPK pathway dysregulation including NF1-mutated tumors. Many tumors associated with the NF1 phenotype can be difficult to treat surgically thus development of further pharmacologic interventions is necessary. Methods: A CRISPR/Cas9 mediated NF1 KO was derived from human immortalized Schwann cells and utilized as a tumor model. Autophagy inhibition was achieved pharmacologically by chloroquine (CQ) and genetically via shRNAi of ATG5 and ATG7. Trametinib was used for MEK inhibition. Cell growth and viability were determined by Incucyte, Cell Titer-Glo luminescent assay, and colony-formation assays. Protein expression was measured by western blot. Results: We demonstrate increased autophagic activity in NF1 KO cell as compared to control lines both at baseline and in response to cellular stress. Furthermore, we describe that NF1 KO cells exhibit increased sensitivity to CQ alone, CQ in combination with trametinib, and shRNAi-mediated autophagy inhibition in combination with trametinib. Conclusion: Here, we describe increased autophagic dependence of NF1 mutated tumors and demonstrate increased tumor sensitivity to autophagy inhibition both alone and in combination with MEK inhibition. These findings indicate that autophagy inhibition via CQ may be an effective adjunctive treatment for NF1 mutated tumors and suggests that diverse CNS tumor types with MAPK pathway dysregulation are susceptible to autophagy inhibition. Clinical investigation of combined MEK and autophagy inhibition has the potential to improve outcomes for NF1 patients with CNS tumors.

#### RARE-19. NETWORK AND DEEP LEARNING INFERENCE IN SINGLE CELL RNA SEQUENCING REVEAL DETAILED TRANSCRIPTIONAL SIGNATURES CONGRUENT WITH MOLECULAR UNDERSTANDING OF ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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Adamantinomatous Craniopharyngioma (ACP) is a highly morbid, cellularly heterogeneous pediatric tumor arising in the sellar/suprasellar region of the brain. This cellular heterogeneity makes ACP an ideal candidate for study using single-cell RNA-sequencing (scRNA-seq). We collected a 10,000 cell scRNA-seq dataset on the 10X v3 platform, from 6 unique patients. Using the industry standard Seurat software package, we identified 34 unique cell clusters. By crossing the results of two separate expert curated cellular reference atlases (Azimuth and scHCL), we determined that 33 of these cell types were immune-related (e.g., T cells, monocytes, etc.) or histologically related (e.g., glial cells). The remaining 2,048 cells were inferred to be ACP driver cells. Rigorous statistical testing of third-generation graph topology-based network enrichment methods utilizing the Reactome database supported this conclusion. In order to identify effective antitumor therapies, it is critical to understand the temporal evolution of tumor cell behavior. Computational solutions that describe the potential lifecycle of tumor cells have been derived using scRNA-seq datasets. Using a well-established method, Monocle3, we generated a potential model of temporal evolution of the ACP driver cell population. To identify a specific transcriptional “point-of-no-return” for ACP driver cells, which may help define a rational target for intervention, we created a custom probabilistic Deep Learning framework in the form of a Convolutional Variational Autoencoder (CVAE). By applying this CVAE to our data, we identified 31 anomalous transcripts, each of which was aberrantly active at all times or demonstrated a temporal pattern of anomalous activity. Strikingly, this small list – representing roughly 0.15% of the protein coding genome – aligns closely with extant data describing the molecular behavior of ACP. This work provides a novel transcriptome benchmark for comparison of *in vitro* models, a deeper understanding of ACP heterogeneity, as well as a generalizable approach for scRNA-seq analysis.