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Comparative gene expression and mutational profiling of neuroendocrine tumors and neuroendocrine carcinomas in relation to clinical outcomes

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OBJECTIVES/GOALS: Neuroendocrine malignancies are heterogeneous cancers with varied clinical outcomes, yet the molecular landscape driving this heterogeneity has not been fully characterized. Here, we investigate the gene expression and mutational profiles of neuroendocrine malignancies to better understand the underlying biology and therapeutic targets. METHODS/STUDY POPULATION: Patients with neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) treated at Cleveland Clinic (2000–2022) with molecular profiling (n = 66) were identified. Mutational and gene expression profiles were abstracted from electronic health records (EHR). Clinico-pathological characteristics and overall survival (OS) were obtained from EHR. Statistical analyses were performed by R v.4.0.5 and R package Limma for differential gene expression, as well as Chi-square, Fisher's exact, and Wilcoxon rank sum tests. RESULTS/ANTICIPATED RESULTS: The cohort consisted of 38 cases with NEC, 18 NET g3, and 10 NET g1/2. EZH2 and cyclin E1 were differentially over-expressed in NEC vs. NET ($p < 0.05$), while PTEN and MSLN were differentially under-expressed in NEC vs. NET ($p < 0.005$). Several recurrent alterations co-segregated with aggressive histology (NEC vs. NET): TP53 (p 60. Also, there was no difference in gene expression profiles between the two age groups among NETs or NECs. DISCUSSION/SIGNIFICANCE OF IMPACT: This study explores the molecular landscape of NETs and NECs, revealing distinct gene expression and mutation profiles related to clinical outcomes. High expressions of cyclin D1 and EGFR were significantly associated with improved 2-year OS in NECs, highlighting potential therapeutic targets. Future studies are needed to validate these findings.

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Surface-based deep learning model assessing brain aging after intracranial radiation for brain metastases

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OBJECTIVES/GOALS: Cognitive decline is a known sequalae of intracranial radiation in the treatment of brain metastases. In this study, we investigate global structural changes in the brain akin to accelerated aging and compare aging kinetics between patients treated with whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). METHODS/STUDY POPULATION: This retrospective study consists of patients with brain metastases treated with WBRT and SRS at our institution. Brain MRI images collected prior to radiation therapy and at approximately three and six months following radiation will be analyzed, excluding patients with evidence of worsening disease burden in the brain. Surface morphology of the cerebral cortex and sub-cortical structures will be extracted using Freesurfer and converted to graphs. Data will then be input into a validated graph convolutional neural network model to estimate brain age at each time point. A generalized linear model will be used to estimate the aging pace between baseline and follow-up for each subject within the whole brain as well as the sub-cortical structures, which will be compared between WBRT and SRS treatment groups. RESULTS/ANTICIPATED RESULTS: We anticipate that intracranial radiation will accelerate brain aging to a greater extent following WBRT compared to SRS. Additionally, this accelerated aging will occur globally in the whole brain as well as within individual substructures, including the cerebral cortex, nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will demonstrate structural changes in the brain analogous to accelerated aging, supporting its potential use as an imaging biomarker to monitor cognitive decline after radiation therapy. Future work will explore the relationship between structural brain aging and assessments of neurocognitive function.

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Identification of novel genetic risk factors for cerebral amyloid angiopathy and characterization of the implicated LINC-PINT locus

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OBJECTIVES/GOALS: Cerebral amyloid angiopathy (CAA) characterized by the accumulation of amyloid-beta in the cerebrovasculature, affects blood vessel integrity leading to brain hemorrhages and an accelerated cognitive decline in Alzheimer's disease patients. In this study, we are conducting a genome-wide association study to identify genetic risk factors for CAA. METHODS/STUDY POPULATION: We genotyped 1253 additional AD cases using and curated existing genome-wide genotype data from 110 AD and 502 non-AD donors from the Mayo Clinic Brain Bank. We performed QC and imputation of all datasets. We conducted GWAS in AD only (N = 1,363), non-AD only, as well as the combined cohort (N = 1,865) by testing imputed variant dosages for association with square root transformed CAA using linear regression, adjusting for relevant covariates. To assess associations in the context of major CAA risk factors, we performed interaction analysis with APOEe4 presence and sex; and pursued stratified analyses. We collected peripheral gene expression measures using RNA isolated from 188 PAXgene tube samples of 95 donors collected across multiple time points. More than 1/3 of these participants have MRI measures collected. RESULTS/ANTICIPATED RESULTS: Variants at the APOE locus were identified as the most significant in our study. In addition, several other variants with suggestive association were found under the main model adjusting for AD neuropathology (Braak and Thal). LINC-PINT splice variant remained associated with lower CAA scores in AD cases without the APOEe4 risk allele. To enhance the robustness of our findings, we are pursuing further expansion of our study cohort. In the periphery, we expect to identify expression changes associated with neuroimaging indicators of CAA and determine if variants and genes discovered via GWAS are implicated in these changes. DISCUSSION/SIGNIFICANCE OF IMPACT: We expect this study will provide further insight into the genetic

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architecture underlying risk for CAA both in the context of significant AD pathology and without. Characterization of genetic variants and functional outcomes in the context of neuropathology may lead to new avenues of research aimed at identifying biomarkers and therapies to treat CAA

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A retrospective analysis of varying thresholds of baseline lung allograft dysfunction in bilateral lung transplant recipients*

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OBJECTIVES/GOALS: Baseline lung allograft dysfunction (BLAD) is defined as the failure to attain normal lung function after transplant and has been associated with impaired survival. BLAD has no consensus definition and assessment of varying thresholds of abnormality may identify an impact on survival or development of chronic lung allograft dysfunction (CLAD). METHODS/STUDY POPULATION: This is a retrospective cohort analysis of bilateral lung transplant recipients who were transplanted between 1/1/2012 and 12/31/2022 who have complete pulmonary function data posttransplant. Thresholds of BLAD including percent predicted levels of FEV1 and FVC at 80%, 75%, 70%, 65%, and 60% were assessed. Outcomes evaluated include survival, development of CLAD, and association of key risk factors with the development of BLAD including donor, recipient, operative, and postoperative characteristics. RESULTS/ANTICIPATED RESULTS: Totally, 680 bilateral lung transplant recipients were identified. Prevalence of BLAD ranged from 41.9% to 9.7% at specified thresholds. We anticipate performing survival analyses and evaluating development of CLAD in patients with BLAD at varying thresholds. We are assessing key donor, recipient, operative, and postoperative variables for association with BLAD. Preliminary analyses demonstrate significant associations of BLAD with recipient-donor height mismatch, prolonged mechanical ventilation time posttransplant, increased length of hospitalization posttransplant, the use of cardiopulmonary bypass intraoperatively and surgical allograft downsizing. DISCUSSION/SIGNIFICANCE OF IMPACT: A threshold of BLAD at 70% predicted FEV1 and FVC or lower suggests importance for developing CLAD. Key characteristics associated with BLAD suggest importance of height mismatch, operative complexity, frailty, and severity of disease at time of transplant and immediately postoperatively.

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Characterizing water transfer rate in the young and elderly using diffusion prepared and multi-echo arterial spin labeling MRI

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OBJECTIVES/GOALS: Our study's overarching goal is to characterize the relationship between water transfer rate (Kw) across the blood–brain barrier (BBB) as measured by diffusion prepared (DP) and multi-echo (ME) ASL in two cohorts that have been shown to have regionally different water transfer rates due to underlying changes in BBB physiology. METHODS/STUDY POPULATION: Ten young, healthy participants (aged 21–30 years, 4f) and 12 elderly participants (aged 66–84 years, 8f) underwent MRI scans on a 3T Siemens Prisma scanner. Structural scans, along with DP and ME ASL, were acquired from each of the participants. The order of the DP and ME ASL sequences was reversed in half the participants to account for ordinal bias. FreeSurfer was used to segment the structural image into respective gray matter, white matter, and deep cortical gray regions to perform region of interest (ROI) analysis. RESULTS/ANTICIPATED RESULTS: We are still in the project's analysis phase. The anticipated result is that we will see different water transfer rate (Kw) patterns between the old and young groups and between the two sequence groups. DISCUSSION/SIGNIFICANCE OF IMPACT: The significance of the results is that we can answer two questions: 1) if there are any differences between water transfer rates in the two age groups and 2) whether there are any variations in performance differences between the sequences.

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Safety and feasibility of transcranial magnetic stimulation in infants with perinatal brain injury: A step toward early clinical translation*

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OBJECTIVES/GOALS: To determine the safety and feasibility of single-pulse transcranial magnetic stimulation (spTMS) for assessing corticospinal tract (CST) excitability and integrity in infants with perinatal brain injury, bridging foundational neuroscience to potential early diagnosis and clinical interventions during critical neuroplasticity periods. METHODS/STUDY POPULATION: Nineteen infants with perinatal brain injury underwent 1–3 spTMS sessions at three developmental time points: 3–6 months, 12 ± 1 month, and 18 ± 1 month. spTMS targeted the primary motor cortex to elicit motor-evoked potentials (MEPs), recorded via electromyography (EMG) from bilateral wrist flexor muscles. Safety monitoring included heart rate (HR), respiratory rate (RR), the Modified Behavioral Pain Scale (MBPS), and caregiver feedback. Feasibility was evaluated based on the ability to elicit MEPs, the number of trials that elicited MEPs, and procedure tolerability. Pre- and post-spTMS physiological and behavioral data were analyzed using linear mixed-effects models (LMEM) to account for repeated measures within subjects. RESULTS/ANTICIPATED RESULTS: Thirty-five spTMS sessions were conducted in 19 infants (mean age 8.75 ± 5.12 months) with perinatal brain injury, delivering 1936 pulses with a median inter-pulse interval of 24.7 seconds. Analysis with LMEM found no significant changes in HR (mean difference = 0.51 bpm, $p = 0.81$) or RR (mean difference = 0.69 breaths/min, $p = 0.66$). MBPS scores showed a small statistically significant increase (mean difference = 0.57, $p = 0.046$), but overall remained low (mean score change from 1.94 to 2.51 on 0–10 scale). The median change score was 0, and 18/35 sessions showed no change in MBPS, indicating low discomfort with TMS. No adverse events were reported during or after the sessions. The feasibility of eliciting MEPs in this population was confirmed, with 235 MEPs identified in 17/19 participants. DISCUSSION/SIGNIFICANCE OF IMPACT: Understanding neurodevelopment after injury is crucial for early diagnosis and targeted rehabilitation. Our study demonstrates that spTMS is a safe, feasible

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