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

Bahar Laderian[1], Yanwen Chen[2] and Prabhjot Singh Mundi[3]
[1]Albert Einstein College of Medicine; [2]Case Western Reserve University and [3]Columbia University Medical Center

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

Stephanie Zhao[1], Zong Fan[2], Timothy J. Mitchell[3], Tammie L.S. Benzinger[1], Nikhil Rammohan[1] and Clifford G. Robinson[1]
[1]Washington University in St. Louis; [2]University of Illinois Urbana-Champaign - and [3]Washington University in St. Louis Hua Li

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

Merve Atik[1], Joseph S. Reddy[3], Thuy Nguyen[2], Katie D. Sotelo[2], Frederick Q, M. Minerva, Carrasquillo, Jonathan Graff-Radford[5], Neil R, Graff-Radford[6], Kejal Kantarci[4], Michael DeTure[2], Dennis W. Dickson[2], Mariet Allen[2], Nilüfer Ertekin-Taner[2,6] and
[1]Mayo Clinic Graduate School of Biomedical Sciences, Jacksonville, FL, USA; [2]Department of Neuroscience, MayoClinic, Jacksonville, FL, USA; [3]Department of Quantitative Health Sciences,Mayo Clinic, Jacksonville, FL, USA; [4]Department of Radiology, Mayo Clinic, Rochester, MN, USA; [5]Mayo Clinic, Neurology, Rochester, MN, USA, and [6]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

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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