Differential DNA Methylation Patterns Support Utilization of Brain Derived Neuropathic Factor as a Biomarker for Cancer-Related Cognitive Impairment

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Introduction

- Growing evidence has shown that decreasing circulating brain derived neuropathic factor levels (BDNF) are associated with an increased likelihood of cancer related cognitive impairment (CRCI)
- Researchers suggest BDNF and broader neurotrophin pathways promote neuronal plasticity to create resilience to harmful toxicities
- To further explore these relationships, we evaluated and compared DNAm patterns relative to measured cognitive function outcomes and circulating BDNF levels

Objective

Evaluate DNA Methylation (DNAm) patterns associated with BDNF expression and measured cognitive function outcomes in cancer patients and assess the extent the support utilization of BDNF as a biomarker in CRCI research

Methods

- **Study Design:**
  - Adult and Young Adult(AYA) cancer patients scheduled to receive Chemotherapy Treatment
  - Longitudinal, prospective study with 5 timepoints over the course of 1 year
- **Outcomes:**
  - Circulating BDNF Levels
  - Measured cognitive function outcomes
- **DNA Methylation Measurements**
  - Illumina Epic Array Chip on blood samples
- **Analysis Approaches:**
  - *Identification of differentially methylated positions (DMP) relative to study outcomes*
    - Linear mixed models, independently conducted for each DNAm site
      - *Outcome~ measured DNAm + Covariates*
    - Significant site: BH corrected (q-value) less than 0.2
      - Assessed ~ 700,000+ DNAm sites
  - *Identification of significantly enriched pathways*
    - Pathways considered were from KEGG and GO repositories
    - Uses genes from DMPs associated with each outcome
    - Pathway enrichment assessed by hypergeometric test
      - Enriched pathway: corrected (q-value) less than 0.2

RESULTS

Table 1: Patient Population

Demographics	
Total Patients	n= 51
Mean (Median) Age	32.5 (34)
Chinese Descent	76.5% (n= 39)
Graduate Degree	58.8% (n= 30)
Male Sex	39.2% (n= 20)
Cancer Therapy	
Radiation	51% (n=26)
Doxorubicin	27.5% (n=14)
Platinum	66.7% (n=34)
Taxanes	25.5% (n=13)

Figure 1:Study Design

- Total of 177 Blood samples with concurrent Clinical Data

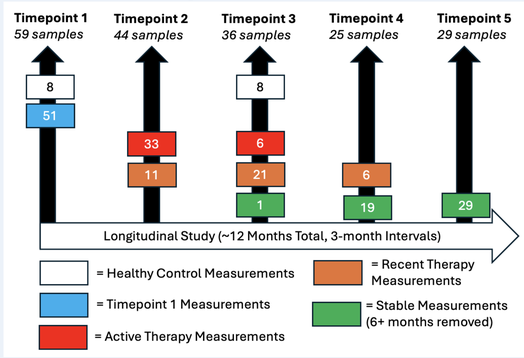

Table 3: Differentially Methylated Positions and Regions Associated with Neurotophin Signaling and Production

Pathway	**Implicated Methylation Sites and Regions**
Neurotrophin Signaling Pathway **HSA:04722** n= 126 genes	*FactCog Score*, **PIK3CD** (cg26573321, chr 1, pos= 9711663) *FactCog Score*, **RPS6KA2** (cg19231371, chr 6, pos= 167196254) *Memory RCI*, **ATF4** (cg07080428, chr 22, pos= 39915234) *Memory RCI*, **CAMK2A** (cg08631650, chr5, pos= 149669813) *Memory RCI*, **GABI** (cg01601573, chr4, pos= 144256835) *Memory RCI*, **SH2B3** (cg01831767, chr12, pos= 111874281) *Response RCI*, **SH2B2** (cg01723606, chr7, pos= 101944275; cg07512361, chr7, pos= 101944430) *Executive Function RCI*, **RAP1A** (cg24160066, chr1, pos= 112161864) *Executive Function RCI*, **RAP1A*** **(chr 1, 3 total probes,** pos= 112161618- 112161865) *Multi-Task RCI*, **HRAS** (cg05798318, chr11, pos= 536758), *Multi-Task RCI*, **SHC3** (cg10242971, chr9, pos= 91692850)
Neurotrophin Production **GO:0032898** n= 5 genes	*FactCog Score*, **NPY** (cg01656438, chr7, pos= 24329741) *Memory RCI*, **ADORA1** (cg00256767, chr1, 203096899; cg04822851, chr1, 203095988; cg07232945, chr1, 203096570; cg12794758, chr1, 203097234; cg19315653, chr1, 203096230; cg27480064, chr1, 203097247) Memory RCI, **ADORA1*** **(chr 1, 6 total probes, pos=** 203096153- 203096684) *Circulating BDNF*, **PCSK6** (cg15587362, chr15, pos= 101986985)

Table 4: Overlapping Enriched Pathways relative to cognitive outcomes and BDNF Levels

Name	***ID***	***Total Pathways***	***Specific Pathways***
synapse	GO:0045202	4	Memory*, Factcog*, Response, Multitask*, BDNF
collagen-containing extracellular matrix	GO:0062023	3	Memory*, Factcog, Response
external encapsulating structure	GO:0030312	3	Memory*, Factcog, Response*
extracellular matrix	GO:0031012	3	Memory*, Factcog, Response*
glutamatergic synapse	GO:0098978	3	Memory*, Factcog, Multitask*, BDNF
neuron projection	GO:0043005	3	Memory*, Factcog, Response, BDNF

Discussion

- **Summary:**
  - We recruited a diverse cohort of AYA cancer patients, collecting concurrent clinical and
  - Longitudinal measurements reflect a diverse trajectory with respect to cancer treatment, including prior to, during, and well after active treatment
  - Implicated DMPS and DMRs significantly associated with cognitive outcomes demonstrate support Neutrophin Signaling as a player in CRCI etiology
  - Significant DNAm patterns relative to BDNF production further support circulating BDNF Levels as biomarkers for CRCI care
  - Enriched pathways similarities support exploration of DNAm derived markers in the future, representative of neurotrophin activity and neuronal function
- **Potential Follow-up Studies**
  - Validate observed epigenetic associations with follow up studies
    - Integrate a multi-omics approach
  - Explore potential of DNAm based biomarkers as opposed to protein biomarkers

Conclusion

Our findings demonstrate that observed DNAm measurements can be utilized in biomarker research. Observed DNAm patterns relative to BDNF have significant expected associations with neuronal function, structure, and resilience with respect to implicated genes and broader pathways. Patterns relative to cognitive function outcomes further demonstrate that they are influenced by neuronal health, and that biomarkers that reflect that may be invaluable.