Title:

Genetic Susceptibility to Cognitive Impairment among Pediatric Cancer Survivors

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Background:

Advances in treatment for pediatric cancers have led to vastly improved outcomes where survivors can live well into adulthood. Unfortunately, cognitive and behavioral development is adversely impacted by curative therapies; this is especially true for children treated for brain tumors. However, whether underlying genetic predisposition contribute to these impairments is not well understood.

Materials and Methods:

Our study included 1,315 pediatric cancer survivors, including survivors of brain tumors, of European ancestry with clinical data and follow-up cognitive testing from the Childhood Cancer Survivor Study (CCSS). The CCSS Neurocognitive Questionnaire (CCSS-NCQ) was used to assess cancer survivors' working memory, emotional regulation, organization, and task efficiency. Impairment was defined as an CCSS-NCQ score in the worst 10th percentile of normative data. Patients' blood/saliva samples were genotyped and then imputed with the Haplotype Reference Consortium r1.1 or 1000 Genomes phase 3 reference panel. Common variants (MAF>0.01) were considered for genome-wide association studies (GWAS). Logistic regression using Plink 1.9 was used to model each cognitive impairment, adjusting for the first four genetic principal components, age at diagnosis, age at follow-up, sex, diagnosis, radiation therapy, anxiety score, depression score, vitality score, and the presence of other neurologic conditions. GWAS variants were considered significant at $p<10^{-7}$.

Results:

The median age was 9 years old (IQR: 4, 14) at cancer diagnosis and 30 years old (IQR: 26, 35) at CCSS-NCQ assessment. Pediatric cancers included central nervous system malignancies (N=325), leukemia (N=228), Hodgkin lymphoma (N=182), Wilms tumor (N=136), bone cancer (N=131), non-Hodgkin lymphoma (N=121), neuroblastoma (N=112), and soft tissue sarcoma (N=80).

The analysis for working memory impairment included 284 cases, identifying three intergenic loci (6q25.3, 9q22.1, 12q24.32). Emotional regulation impairment was present in 178 patients and significant alterations to seven loci (1p31.1, 1q23.3, 3q13.13, 10p11.1, 13q33.1, 14q13.3, 15q14). Four loci harbored variants among the 250 cases with organization impairment (5p14.1, 5q35.3, 10q22.1, 20q11.22). Impairment in task efficiency was present in 249 patients and found significant alteration on five loci (1q44, 3q13.31, 4p15.32, 9q32, 10p12.1).

Conclusions:

Our GWAS identified several genes implicated in cognitive impairment across pediatric cancer survivors. A considerable portion of these cognitive deficits were among children with central nervous system cancers, where over a quarter of cancer survivors had impaired task efficiency and working memory. The task efficiency GWAS identified variants on *LSAMP* and *HSDL2*, *LSAMP* is involved in neuronal and limbic system development. *HSDL2* has been linked with epilepsy and several cancers. *SDHC* and *HSD17B7P2* were associated with emotional regulation impairment; *SDHC* is a known tumor suppressor linked with hereditary paraganglioma. *HSD17B7P2* has been associated with Alzheimer's disease incidence and plays a role in embryonic brain development. Alterations to *MACROH2A2* and *PIGU* were linked to

organization impairment, *MACROH2A2* expression has been associated with survival in glioblastoma. Finally, *PIGU* is associated with significant intellectual disability in children.

Future studies are planned to replicate and functionally validate the potential susceptibility loci identified in our GWAS. Improved characterization of survivors at elevated risk of adverse neurocognitive outcomes are important to guide the development of risk-stratified neuroprotective strategies.