Whole genome cell-free tumor DNA mutational signatures for noninvasive monitoring of pediatric brain cancers

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INTRODUCTION

Liquid biopsy offers a noninvasive approach to monitor cancer burden during therapy and surveillance period. However, in pediatric brain cancers, liquid biopsy methods from the blood have been unsuccessful due to a low tumor burden and low number of mutations in coding regions. We hypothesized that a whole genome sequencing (WGS)-derived patient specific mutational signature from a matched tumor-normal WGS can provide a sensitive and specific approach to detect mutations in circulating cell free tumor DNA (ctDNA) and provide blood-based monitoring in pediatric patients with brain tumor.

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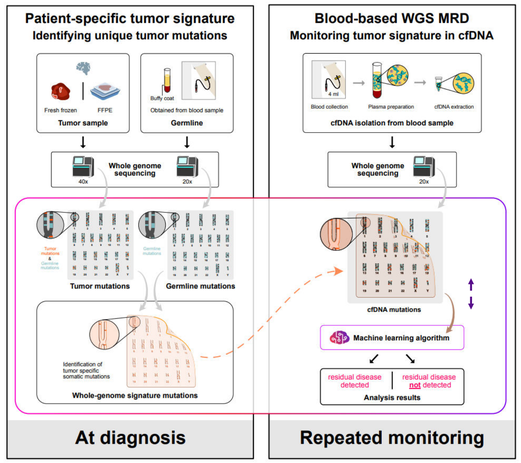
METHOD



All brain tumors were analyzed and molecularly subclassified using whole genome DNA methylation profiling and AI classification. Tumor DNA was extracted from pathology tissue and normal germline DNA from the white blood cells, ctDNA was extracted from 1-2 mL of post-surgery blood samples for each patient at 1-3 available time points. The ctDNA Tumor Fraction (TF) was compared to the clinical status and imaging.

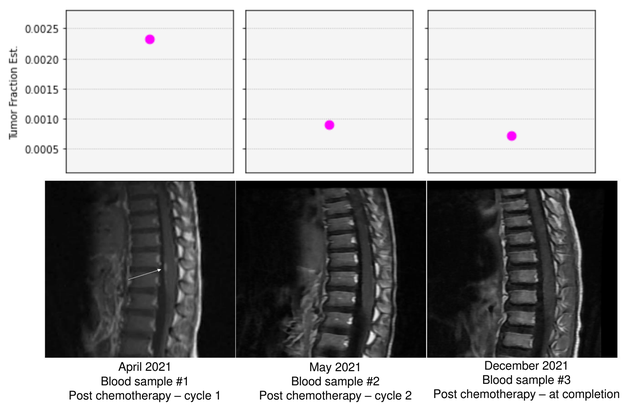
RESULTS

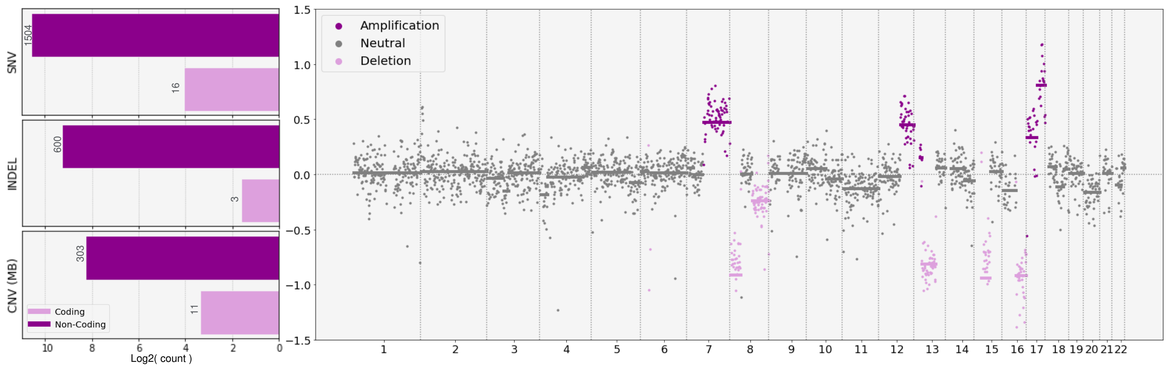
We profiled 7 pediatric brain tumors, including 2 medulloblastomas (one Group 3, one Group 4), 3 pediatric glioblastomas IDH wild-type, 1 ependymoma PFA subtype and one low grade ganglioglioma. Tumor specific signatures were identified and detected in the plasma of 5 patients with clinical disease with a TF range 0.02-0.0005 but not in 2 patients with no tumor at the time of blood collection. In two children with a medulloblastoma and glioblastoma, the decrease of tumor fraction in ctDNA over 2 (TF: 0.002 to 0.0009) and 3 time points (TF: 0.0005 to undetectable), respectively, correlated with response to therapy based on imaging.

CONCLUSIONS

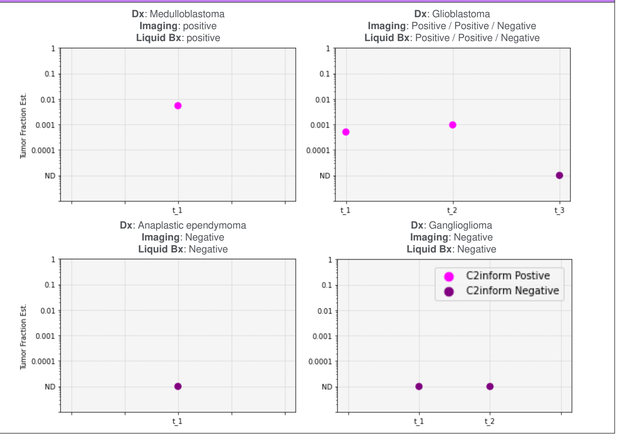
Patient-specific WGS tumor signature in ctDNA from blood can be used for sensitive monitoring of children with brain tumors. Patient specific signatures could be established across various histologic subtypes and were present at the time of diagnosis. This blood based monitoring method is minimally-invasive compared to CSF liquid biopsy testing.

CASE STUDY: 6 y.o. M, Dx of medulloblastoma, Group 4, s/p gross total resection of the cerebral tumor, with spinal leptomeningeal disease
CSF: cytology and ctDNA negative on follow-up





Representative clinical cases



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