# INTRODUCTION

Pineoblastoma (PB) is one of the rarest and most aggressive brain tumors of childhood. PB is considered a "primitive neuroectodermal tumor" (PNET) based on histology, and commonly treated using treatment protocols developed for medulloblastoma. A subset of PBs may occur in the setting of germline mutations involving DICER1, but no next-generation sequencing studies have been published on PB to date, and the genetic drivers of sporadic PB remain unknown.

## METHODS

21 tumor samples with a histological diagnosis of PB (including recurrent/metastatic samples) from 15 patients were included in this study. Matching germline DNA was available from 2 patients. We performed genome-wide methylation array profiling (Illumina Infinium 450k) on all samples, as well as whole-genome (for samples with matching germline DNA) or whole-exome sequencing analysis. Fluorescence in situ hybridization (FISH) and digital droplet PCR (ddPCR) was performed to confirm select focal somatic gains.

## RESULTS

14/18 samples from 9/13 patients analyzed by 450k profiling had a methylation signature similar to previously profiled PBs from a reference cohort. Samples from 4 patients were found to be more consistent with a diagnosis of embryonal tumor with multilayered rosettes (ETMR)-like tumor (non 19q amplified), papillary tumor of the pineal region, or pineal parenchymal tumor of intermediate differentiation, respectively. No mutations in DICER1 or RB1 were found. Homozygous deletions in DROSHA were found in tumors from 3 PB patients. We identified novel and recurrent somatic gains involving chromosomal region 1q21 that were confirmed by FISH and ddPCR in 4/5 PB patients.

## CONCLUSION

Our studies revealed multiple candidate drivers of oncogenesis in PB. We identified novel homozygous deletions in DROSHA, a nuclease involved in microRNA processing. We also identified novel, highly recurrent somatic focal gains involving chromosomal region 1q21, which has been linked to brain growth, autism and schizophrenia, but not previously associated with cancer.