Molecular Inversion Probes (MIPs) Identify Novel Genomic Signatures in Pediatric Brain Cancers

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Abstract

Background: Childhood brain tumors (CBTs) are the most common solid pediatric cancer and the leading cause of pediatric cancer mortality. The majority of CBTs are gliomas, yet we know little about the underlying copy number alterations (CNAs) that lead to their development, progression, and transformation. Molecular inversion probes (MIPs) are a novel, powerful tool for identifying genome-wide CNAs with limited DNA, and have found novel genomic changes contributing to tumorogenesis in other tumors. MIP technology may provide new insight into the molecular causes of low grade gliomas (LGGs).

Objective: To use MIP technology in a pilot study for identification of novel CNAs in pediatric LGGs.

Methods: DNA was extracted from 22 fresh-frozen pediatric gliomas (pilocytic astrocytoma (PA), n=4; WHO grade I; ependymoma, n=2; grade II;ependymoblastoma, grade III; medulloblastoma, n=5) and non-neoplastic brain tissue control samples (n=9). The MIP assay was run using 73M of genomic DNA sample on a customized Affymetrix MIP 350K platform with probes hybridizing throughout the genome to perform a complete analysis.

Results: Non-neoplastic brain tissue (n=9). Pilocytic astrocytoma (n=14) WHO grade I (15 affected genes/78 total), CN value ≥ 2.4. Filtered for probe call rates ≤ 90% and RSD ≥ 20%.

Conclusions: This is the first molecular profile of pediatric LGGs using MIP technology. The limited amount of tissue sample available from pediatric LGGs makes MIP technology ideal for this type of study. Our pilot study revealed known and novel regions of CNAs in pediatric LGGs, including COL1A1 previously implicated in HGGs. We also found that LGGs contain a known and novel regions of CNAs in pediatric LGGs, including COL1A1 which overlaps with our observed deletion. This is the first molecular profile of pediatric LGGs using MIP technology. The limited amount of tissue sample available from pediatric LGGs makes MIP technology ideal for this type of study. Our pilot study revealed known and novel regions of CNAs in pediatric LGGs, including COL1A1 previously implicated in HGGs. We also found that LGGs contain a known and novel regions of CNAs in pediatric LGGs, including COL1A1 which overlaps with our observed deletion.

Figure 1. Molecular Inversion Probe (MIP) structure.

Figure 2. Heat map of region 17q21.33. Amplifications are indicated in red and deletions in blue, copy number plotted on log ratio scale. Grade I tumors shown in rows 19-28, grade II tumors in rows 27 & 28, and normals 1-9 on y-axis.

Table 1. Summary of CNAs listed by biological process. (Data generated with Nexus Copy Number Version 5 by BioDiscovery, Inc.)

Conclusions

- MIPs identified copy number alterations (CNAs) in pediatric LGGs.
- Non integer copy numbers indicated tumor heterogeneity even in low grade tumors.
- Further study with MIP analysis and clinical data may lead to more accurate tumor profiling and outcome prediction.