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Abstracts

LOW GRADE GLIOMA

LG-01. BRAF MUTATION AND CDKN2A DELETION DEFINE A CLINICALLY DISTINCT SUBGROUP OF CHILDHOOD SECONDARY HIGH-GRADE GLIOMA

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PURPOSE: To uncover the genetic events leading to transformation of pediatric low-grade glioma (PLGG) to secondary high-grade glioma (sHGG). METHODS: We retrospectively identified sHGG cases from a population-based cohort of 886 PLGG with very long clinical follow-up. Exome-sequencing and copy number alterations were performed on available samples followed by detailed genetic analysis of the entire sHGG cohort. Clinical and outcome data of genetically distinct subgroups was performed. RESULTS: sHGG was observed in 2.9% of PLGG (26/886). sHGG had a high frequency of non-silent somatic mutations compared to primary pediatric HGG (median 25/exome; $P = .0042$). Alterations in chromatin modifying genes and telomere-maintenance pathways were commonly observed while no sHGG harbored the BRAF-KIAA1549 fusion. The most recurrent alterations were BRAF V600E and CDKN2A deletion in 39% and 57% of sHGG, respectively. Importantly, all BRAF V600E and 80% of CDKN2A alterations could be traced back to their PLGG counterparts. BRAF V600E distinguished secondary from primary HGG ($P = .0023$), while BRAF and CDKN2A alterations were rarely observed in PLGG which did not transform ($P < .0001$ and .0007 respectively). PLGGs with BRAF mutations had longer latency to transformation than wild-type PLGG (median 6.65, 3.5-20.3 years versus 1.59, 0.32-15.9; $P = .0389$). Furthermore, 5-year overall survival was 75%□15% and 29%□12% for children with BRAF mutant and wild-type tumors, respectively ($P = .024$). CONCLUSION: BRAF V600E mutations and CDKN2A deletions constitute a clinically distinct subtype of sHGG. The prolonged course to transformation for BRAF V600E PLGGs provides an opportunity for surgical interventions, surveillance and targeted therapies to mitigate the outcome of sHGG.