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Whole Genome Sequencing Unravels Novel Genomic Variants and Their Impact on Tumor Phenotypes in High-Risk Neuroblastoma

Neuroblastoma (NB) is a pediatric solid tumor, with a median diagnosis age of 18 months. Its presentation varies widely, ranging from low-risk tumors to aggressive disease in high-risk cases with a 5-year survival rate of 50%. Despite numerous identified genomic alterations, the current understanding of NB mutational landscape does not fully explain its heterogeneity. We analyzed Whole Genome Sequencing (WGS) and RNA-seq data from two independent NB cohorts TARGET (n = 136) and EGA (n = 180). We aim to provide a comprehensive overview of NB genomic alterations, focusing on rearrangements (translocation and insertion). We developed pipelines to detect and analyze somatic single nucleotide variants (SNVs), copy-number alterations (CNAs), structural variants (SVs), and germline SNVs. We identified previously unreported SNVs in 3 cancer-related genes: ESR1, MYH9, and SKI. Notably, SKI was overexpressed in the low/intermediate-risk group across both cohorts. We confirmed known CNAs in both high and low/intermediate-risk groups and identified new alterations not previously associated with clinical parameters (chr1 gain, chr2 gain, chr11 loss, chr12 gain, and chr19 loss). The presence of at least one of these aneuploidies predicted survival outcomes, both independently and in multivariate models considering age at diagnosis, INSS stage, MYCN status, and dataset origin. Furthermore, we discovered 5 novel low-frequency SVs in high-risk tumors. These SV breakpoints overlapped with 171 genes, with 12 genes common to both datasets. These genes are involved in synaptic plasticity and in various neurological disorders. Tumors with at least one SV exhibited distinct gene-expression, unique mutational signatures, higher genomic instability and increased tumor mutational burden. Additionally, tumors carrying these SVs were enriched in pathogenic/likely pathogenic germline SNVs in the homologous-recombination (HR) pathway, linking pathway deficiencies to genomic instability. Overall, our analysis identifies novel molecular alterations, define the phenotypes of tumors with SVs, and suggests that rare germline variants in the HR pathway may contribute to genomic instability. These findings could improve NB clinical stratification and our understanding of the genetic predisposition to this tumor.

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