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ITCC-P4: Genomic profiling and analyses of pediatric patient tumor and patient-derived xenograft (PDX) models for high throughput *in vivo* testing

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Abstract

Advancements in state-of-the-art molecular profiling techniques have resulted in better understanding of pediatric cancers and driver events. It has become apparent that pediatric cancers are significantly more heterogeneous than previously thought as evidenced by the number of novel entities and subtypes that have been identified with distinct molecular and clinical characteristics. For most of these newly recognized entities there are extremely limited treatment options available. The ITCC-P4 consortium is an international collaboration between several European academic centers and pharmaceutical companies, with the overall aim to establish a sustainable platform of >400 molecularly well-characterized PDX models of high-risk pediatric cancers, their tumors and matching controls and to use the PDX models for in vivo testing of novel mechanism-of-action based treatments. Currently, 251 models are fully characterized, including 182 brain and 69 non-brain PDX models, representing 112 primary models, 92 relapse, 42 metastasis and 4 progressions under treatment models. Using low coverage whole-genome and whole exome sequencing, somatic mutation calling, DNA copy number and methylation analysis we aim to define genetic features in our PDX models and estimate the molecular fidelity of PDX models compared to their patient tumor. Based on DNA methylation profiling we identified 43 different tumor subgroups within 18 cancer entities. Mutational landscape analysis identified key somatic and germline oncogenic drivers. Ependymoma PDX models displayed the C11orf95-RELA fusion event, YAP1, C11orf95 and RELA structural variants. Medulloblastoma models were driven by MYCN, TP53, GLI2, SUFU and PTEN. High-grade glioma samples showed TP53, ATRX, MYCN and PIK3CA somatic SNVs, along with focal deletions in CDKN2A in chromosome 9. Neuroblastoma models were enriched for ALK SNVs and/or MYCN focal amplification, ATRX SNVs and CDKN2A/B deletions. Tumor mutational burden across entities and copy number analysis was performed to identify allele-specific copy number detection in tumor-normal pairs. Large chromosomal aberrations (deletions, duplications) detected in the PDX models were concurrent with molecular alterations frequently observed in each tumor type -isochromosome 17 was detected in 5 medulloblastoma models, while deletion of chromosome arm 1p or gain of parts of 17q in neuroblastomas which correlate with tumor progression. We observe clonal evolution of somatic variants not only in certain PDX-tumor pairs but also between disease states. The multi-omics approach in this study provides insight into the mutational landscape and patterns of the PDX models thus providing an overview of molecular mechanisms facilitating the identification and prioritization of oncogenic drivers and potential biomarkers for optimal treatment therapies.