

Multomics analysis of pediatric solid tumors within the INFORM precision oncology study: From functional drug profiling to biomarker identification.

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Background: Within the INFORM (INdividualized Therapy FORe Relapsed Malignancies in Childhood) registry over 1200 childhood malignancies were molecularly profiled using next generation sequencing to identify therapeutic targets. Nevertheless, high evidence targets were only detected in 5% of cases and only 50% of the patients were identified with druggable pathways, while the remaining cases lacked druggable alterations. Thus, an ex-vivo functional drug response profiling platform for pediatric solid tumors has been established within the INFORM program to identify novel biomarkers and unravel molecular mechanisms associated with drug response profiles for clinical translation. **Methods:** Solid tumors from 97 paediatric patients were screened against a library of 76 drugs. A quality control classification decision tree was designed to select the samples for further analysis. Whole exome sequencing, low-coverage whole genome sequencing, and RNA-seq were used to analyze the molecular profiles of the samples. Molecular features were filtered to retain oncogenic and druggable events. Five data feature views (mutations, mRNA, gene fusions, CNVs, and drug responses) were used to train a Multi-Omics Factor Analysis (MOFA) model to identify prominent latent factors. **Results:** 81 samples passed the quality control inclusion criteria of which 76 samples had available omics data profiles. Quantitative drug profiling measurements were reported using the selective asymmetric drug sensitivity score.- The multi-omics analysis captured five entity-specific omics signatures of Ewing sarcoma, Wilms tumor, BCOR sarcoma, neuroblastoma and ependymoma. Moreover, the analysis revealed sensitivity to navitoclax in neuroblastoma samples with PHOX2B-GATA3 overexpression, and an association between MEK inhibitor sensitivity and an expression signature in Wilms tumors. **Conclusions:** The combination of functional drug and multi-omics profiling enabled the identification of novel biomarkers for drug sensitivities in pediatric solid tumors. As we continue to expand the number of patient samples evaluated with our drug sensitivity platform, this dataset will provide insights for novel drug targets, and could unravel key molecular events and mechanisms acting towards personalized therapies. Research Sponsor: German Cancer Consortium (DKTK), the German Cancer Aid (DKH), the German Childhood Cancer Foundation (DKS), the German Cancer Research Center (DKFZ) and "Ein Herz für Kinder", Other Foundation.