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Identification of SMARC deficient pediatric tumors for drug screening/testing

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Among pediatric cancers, solid tumors accounts for approximately with 30% of cases. Central nervous system (CNS) tumors are the second most frequent type (15%) and the first cause of death. Others solid tumors are distributed among neuroblastoma (6%), Wilms tumor (5%), non-Hodgkin lymphoma (4%), rhabdomyosarcoma (3%), retinoblastoma (3%), osteosarcoma (3%), Ewing's sarcoma (1%), germ cell tumors (5%), hepatoblastoma and others. Cure rate is ca reach 90% in ideal conditions, but it is the first cause of death by disease worldwide, including in Brazil. For the survivors, patients are at high risk of long-term toxicity and treatment-associated comorbidities that affect their quality of life. The incorporation of molecular markers in tumor diagnosis has improved risk stratification, which affects patient prognosis. The World Health Organization already adopted the methylation profiles as the gold standard method for classification of CNS tumors, as methylomes allow refining their classification, affecting the clinical management and opening the possibility of alternative treatments. Here, we evaluated a cohort of 242 pediatric solid tumors from individuals treated at a reference hospital in Brazil. Bisulfite-converted DNA was hybridised in the Illumina MethylationEPIC BeadChip arrays. Methylation profiles were classified in molecular entities using the DKFZ/Heidelberg CNS/sarcoma tumor package (v12.5), and the copy number alterations (CNAs) were characterized. Similar to other studies, CNS samples were classified with high-confidence classifier score (>0.84) in 80.8% of the cases. For sarcomas, 63.9% of samples were classified with high-confidence classifier score, and others embryonal tumor, the percentage was 77.7%. CNA was used to identify deletions in SMARCA1, SMARCA2, SMARCA4, SMARCA5 and SMARCB1. Deletions in genes from the SMARC family are associated poor prognosis for the patients. They are more commonly reported in high-risk tumors, such as atypical teratoid rhabdoid tumor and rhabdomyosarcomas. We found that 17.4% (42/242) of tumors have at least one SMARC deletion. While we found the more common classes of SMARC deficient tumors, other reported rarer cases, such as osteosarcomas, neuroblastomas, medulloblastomas, ependymomas and others. Smarc-deficient tumors are susceptible to epigenetic drugs. Five epigenetic chemical probes were tested in 3D culture using spheroids from the G401, a primary cell line derived from SMARCB1-deficient teratoide rabdoide (UNC1999, GSK343, A395 Hydrochloride, PFI-3 and SGC-SMARCA-BRDVIII). Once, established chemical probes IC50, primary cells from patient smarc-deficient tumors that were biobanked, will be treated with the chemicals that interfere with this molecular alteration, independent of type tumor.

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