Deep Sequencing in Conjunction with Expression and Functional Analyses Reveals Activation of FGFR1 in Ewing Sarcoma.

A low mutation rate seems to be a general feature of pediatric cancers, in particular in oncofusion gene-driven tumors. Genetically, Ewing sarcoma is defined by balanced chromosomal EWS/ETS translocations, which give rise to oncogenic chimeric proteins (EWS-ETS). Other contributing somatic mutations involved in disease development have only been observed at low frequency. Tumor samples of 116 Ewing sarcoma patients were analyzed here. Whole-genome sequencing was performed on two patients with normal, primary, and relapsed tissue. Whole-exome sequencing was performed on 50 Ewing sarcoma and 22 matched normal tissues. A discovery dataset of 14 of these tumor/normal pairs identified 232 somatic mutations. Recurrent nonsynonymous mutations were validated in the 36 remaining exomes. Transcriptome analysis was performed in a subset of 14 of 50 Ewing sarcomas and DNA copy number gain and expression of FGFR1 in 63 of 116 Ewing
sarcomas. Relapsed tumors consistently showed a 2- to 3-fold increased number of mutations. We identified several recurrently mutated genes at low frequency (ANKRD30A, CCDC19, KIAA0319, KIAA1522, LAMB4, SLFN11, STAG2, TP53, UNC80, ZNF98). An oncogenic fibroblast growth factor receptor 1 (FGFR1) mutation (N546K) was detected, and the FGFR1 locus frequently showed copy number gain (31.7%) in primary tumors. Furthermore, high-level FGFR1 expression was noted as a characteristic feature of Ewing sarcoma. RNA interference of FGFR1 expression in Ewing sarcoma lines blocked proliferation and completely suppressed xenograft tumor growth. FGFR1 tyrosine kinase inhibitor (TKI) therapy in a patient with Ewing sarcoma relapse significantly reduced 18-FDG-PET activity. FGFR1 may constitute a promising target for novel therapeutic approaches in Ewing sarcoma.

Zeitschriftentitel / Abkürzung: Clin Cancer Res
Jahr: 2015
Band: 21
Heft / Issue: 21
Seiten: 4935-46
Sprache: eng
Volltext / DOI: http://doi.org/10.1158/1078-0432.CCR-14-2744
Print-ISSN: 1078-0432
TUM Einrichtung: Kinderklinik und Poliklinik; Institut für Medizinische Mikrobiologie, Immunologie und Hygiene

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Medizinische Mikrobiologie, Immunologie und Hygiene > 2015
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Klinik und Poliklinik für Kinderheilkunde und Jugendmedizin > 2015

entries: