Cooperation of cancer drivers with regulatory germline variants shapes clinical outcomes

Julian Musa, Florencia Cidre-Aranaz, Marie-Ming Aynaud, Martin F Orth, Maximilian M L Knott, Olivier Mirabeau, Gal Mazor, Mor Varon, Tilman L B Hölting, Sandrine Grossetête, Moritz Gartlgruber, Didier Surdez, Julia S Gerke, Shunya Ohmura, Aruna Marchetto, Marlene Dallmayer, Michaela Baldauf, Stefanie Stein, Giuseppina Sannino, Jing Li, Laura Romero-Pérez, Frank Westermann, Wolfgang Hartmann, Uta Dirksen, Melissa Gymrek, Nathaniel D Anderson, Adam Shlien, Barak Rotblat, Thomas Kirchner, Olivier Delattre & Thomas G P Grünewald

Pediatric malignancies including Ewing sarcoma (EwS) feature a paucity of somatic alterations except for pathognomonic driver-mutations that cannot explain overt variations in clinical outcome. Here, we demonstrate in EwS how cooperation of dominant oncogenes and regulatory germline variants determine tumor growth, patient survival and drug response. Binding of the oncogenic EWSR1-FLI1 fusion transcription factor to a polymorphic enhancer-like DNA element controls expression of the transcription factor MYBL2 mediating these phenotypes. Whole-genome and RNA sequencing reveals that variability at this locus is inherited via the germline and is associated with variable inter-tumoral MYBL2 expression. High MYBL2 levels sensitize EwS cells for inhibition of its upstream activating kinase CDK2 in vitro and in vivo, suggesting MYBL2 as a putative biomarker for anti-CDK2-therapy. Collectively, we establish cooperation of somatic mutations and regulatory germline variants as a major determinant of tumor progression and highlight the importance of integrating the regulatory genome in precision medicine.