Année de publication : 2017

Mathieu Chicard, Leo Colmet-Daage, Nathalie Clement, Adrien Danzon, Mylène Bohec, Virginie Bernard, Sylvain Baulande, Angela Bellini, Paul Deveau, Gaëlle Pierron, Eve Lapouble, Isabelle Janoueix-Lerosey, Michel Peuchmaur, Nadège Corradini, Anne Sophie Defachelles, Dominique Valteau-Couanet, Jean Michon, Valérie Combaret, Olivier Delattre, Gudrun Schleiermacher (2017 Dec 2)

Whole-Exome Sequencing of Cell-Free DNA Reveals Temporo-spatial Heterogeneity and Identifies Treatment-Resistant Clones in Neuroblastoma.

Clinical cancer research : an official journal of the American Association for Cancer Research : 939-949 : DOI : 10.1158/1078-0432.CCR-17-1586

Résumé

Neuroblastoma displays important clinical and genetic heterogeneity, with emergence of new mutations at tumor progression. To study clonal evolution during treatment and follow-up, an innovative method based on circulating cell-free DNA (cfDNA) analysis by whole-exome sequencing (WES) paired with target sequencing was realized in sequential liquid biopsy samples of 19 neuroblastoma patients. WES of the primary tumor and cfDNA at diagnosis showed overlap of single-nucleotide variants (SNV) and copy number alterations, with 41% and 93% of all detected alterations common to the primary neuroblastoma and cfDNA. CfDNA WES at a second time point indicated a mean of 22 new SNVs for patients with progressive disease. Relapse-specific alterations included genes of the MAPK pathway and targeted the protein kinase A signaling pathway. Deep coverage target sequencing of intermediate time points during treatment and follow-up identified distinct subclones. For 17 seemingly relapse-specific SNVs detected by cfDNA WES at relapse but not tumor or cfDNA WES at diagnosis, deep coverage target sequencing detected these alterations in minor subclones, with relapse-emerging SNVs targeting genes of neuritogenesis and cell cycle. Furthermore a persisting, resistant clone with concomitant disappearance of other clones was identified by a mutation in the ubiquitin protein ligase Modelization of mutated allele fractions in cfDNA indicated distinct patterns of clonal evolution, with either a minor, treatment-resistant clone expanding to a major clone at relapse, or minor clones collaborating toward tumor progression. Identification of treatment-resistant clones will enable development of more efficient treatment strategies. .

Léa Guerrini-Rousseau, Christelle Dufour, Pascale Varlet, Julien Masliah-Planchon, Franck Bourdeaut, Marine Guillaud-Bataille, Rachid Abbas, Anne-Isabelle Bertozzi, Fanny Fouyssac, Sophie Huybrechts, Stéphanie Puget, Brigitte Bressac-De Paillerets, Olivier Caron, Nicolas Sevenet, Marina Dimaria, Sophie Villebasse, Olivier Delattre, Dominique Valteau-Couanet, Jacques Grill, Laurence Brugières (2017 Nov 30)

Germline SUFU mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis.

Neuro-oncology : 1122-1132 : DOI : 10.1093/neuonc/nox228

Résumé

Germline mutations of suppressor of fused homolog (SUFU) predispose to sonic hedgehog (SHH) medulloblastoma. Germline SUFU mutations have been reported in nevoid basal cell carcinoma syndrome (NBCCS), but little is known about the cancer risk and clinical spectrum.

Céline Chauvin, Amaury Leruste, Arnault Tauziede-Espariat, Mamy Andrianteranagna, Didier Surdez, Aurianne Lescure, Zhi-Yan Han, Elodie Anthony, Wilfrid Richer, Sylvain Baulande, Mylène Bohec, Sakina Zaidi, Marie-Ming Aynaud, Laetitia Maillot, Julien Masliah-Planchon, Stefano Cairo, Sergio Roman-Roman, Olivier Delattre, Elaine Del Nery, Franck Bourdeaut (2017 Nov 16)
High-Throughput Drug Screening Identifies Pazopanib and Clofilium Tosylate as Promising Treatments for Malignant Rhabdoid Tumors.
Cell reports : 1737-1745 : DOI : S2211-1247(17)31539-5

Résumé

Rhabdoid tumors (RTs) are aggressive tumors of early childhood characterized by SMARCB1 inactivation. Their poor prognosis highlights an urgent need to develop new therapies. Here, we performed a high-throughput screening of approved drugs and identified broad inhibitors of tyrosine kinase receptors (RTKs), including pazopanib, and the potassium channel inhibitor clofilium tosylate (CfT), as SMARCB1-dependent candidates. Pazopanib targets were identified as PDGFRα/β and FGFR2, which were the most highly expressed RTKs in a set of primary tumors. Combined genetic inhibition of both these RTKs only partially recapitulated the effect of pazopanib, emphasizing the requirement for broad inhibition. CfT perturbed protein metabolism and endoplasmic reticulum stress and, in combination with pazopanib, induced apoptosis of RT cells in vitro. In vivo, reduction of tumor growth by pazopanib was enhanced in combination with CfT, matching the efficiency of conventional chemotherapy. These results strongly support testing pazopanib/CfT combination therapy in future clinical trials for RTs.

Barbara Hero, Nathalie Clement, Ingrid Øra, Gaelle Pierron, Eve Lapouble, Jessica Theissen, Claudia Pasqualini, Dominique Valteau-Couanet, Dominique Plantaz, Jean Michon, Olivier Delattre, Marc Tardieu, Gudrun Schleiermacher (2017 Nov 15)
Genomic Profiles of Neuroblastoma Associated With Opsoclonus Myoclonus Syndrome.
Journal of pediatric hematology/oncology : 93-98 : DOI : 10.1097/MPH.0000000000000976

Résumé

Opsoclonus myoclonus syndrome (OMS), often called « dancing eyed syndrome, » is a rare neurological condition associated with neuroblastoma in the majority of all childhood cases. Genomic copy number profiles have shown to be of prognostic significance for neuroblastoma patients. The aim of this retrospective multicenter study was to analyze the

genomic copy number profiles of tumors from children with neuroblastoma presenting with OMS at diagnosis. In 44 cases of neuroblastoma associated with OMS, overall genomic profiling by either array-comparative genomic hybridization or single nucleotide polymorphism array proved successful in 91% of the cases, distinguishing tumors harboring segmental chromosome alterations from those with numerical chromosome alterations only. A total of 23/44 (52%) tumors showed an segmental chromosome alterations genomic profile, 16/44 (36%) an numerical chromosome alterations genomic profile, and 1 case displayed an atypical profile (12q amplicon). No recurrently small interstitial copy number alterations were identified. With no tumor relapse nor disease-related deaths, the overall genomic profile was not of prognostic impact with regard to the oncological outcome in this series of patients. Thus, the observation of an excellent oncological outcome, even for those with an unfavorable genomic profile of neuroblastoma, supports the hypothesis that an immune response might be involved in tumor control in these patients with OMS.

Boeva, V., Louis-Brennetot, C., Peltier, A., Durand, S., Pierre-Eugène, C., Raynal, V., Etchevers, H.C., Thomas, S., Lermine, A., Daudigeos-Dubus, E., Geoerger, B., Orth, M.F., Grünewald, T.G.P., Diaz, E., Ducos, B., Surdez, D., Carcaboso, A.M., Medvedeva, I., Deller, T., Combaret, V., Lapouble, E., Pierron, G., Grossetête-Lalami, S., Baulande, S., Schleiermacher, G., Barillot, E., Rohrer, H., Delattre, O., and Janoueix-Lerosey, I. (2017 Sep 1)

Heterogeneity of neuroblastoma cell identity defined by transcriptional circuitries.

Nature Genetics : DOI : 10.1038/ng.3921

Résumé

Neuroblastoma is a tumor of the peripheral sympathetic nervous system, derived from multipotent neural crest cells (NCCs). To define core regulatory circuitries (CRCs) controlling the gene expression program of neuroblastoma, we established and analyzed the neuroblastoma super-enhancer landscape. We discovered three types of identity in neuroblastoma cell lines: a sympathetic noradrenergic identity, defined by a CRC module including the PHOX2B, HAND2 and GATA3 transcription factors (TFs); an NCC-like identity, driven by a CRC module containing AP-1 TFs; and a mixed type, further deconvoluted at the single-cell level. Treatment of the mixed type with chemotherapeutic agents resulted in enrichment of NCC-like cells. The noradrenergic module was validated by ChIP-seq. Functional studies demonstrated dependency of neuroblastoma with noradrenergic identity on PHOX2B, evocative of lineage addiction. Most neuroblastoma primary tumors express TFs from the noradrenergic and NCC-like modules. Our data demonstrate a previously unknown aspect of tumor heterogeneity relevant for neuroblastoma treatment strategies.

Franzetti GA, Laud-Duval K, van der Ent W, Brisac A, Irondelle M, Aubert S, Dirksen U, Bouvier C, de Pinieux G, Snaar-Jagalska E, Chavrier P, Delattre O, (2017 Jun 22)

Cell-to-cell heterogeneity of EWSR1-FLI1 activity determines

proliferation/migration choices in Ewing sarcoma cells.
Oncogene- : DOI : 10.1038/onc.2016.498

Résumé

Ewingsarcomais characterized by the expression of the chimeric EWSR1-FLI1transcription factor. Proteomic analyses indicate that the decrease of EWSR1-FLI1expression leads to major changes in effectors of the dynamics of the actin cytoskeleton and the adhesion processes with a shift from cell-to-cellto cell-matrix adhesion. These changes are associated with a dramatic increase of in vivo cell migrationand invasion potential. Importantly, EWSR1-FLI1expression, evaluated by single-cell RT-ddPCR/immunofluorescence analyses, and activity, assessed by expression of EWSR1-FLI1downstream targets, are heterogeneous in cell lines and in tumours and can fluctuate along time in a fully reversible process between EWSR1-FLI1^{high}states, characterized by highly active cell proliferation, and EWSR1-FLI1^{low}states where cellshave a strong propensity to migrate, invade and metastasize. This new model of phenotypic plasticity proposes that the dynamic fluctuation of the expression level of a dominant oncogene is an intrinsic characteristic of its oncogenic potential.

Sheffield NC, Pierron G, Klughammer J, Datlinger P, Schönegger A, Schuster M, Hadler J, Surdez D, Guillemot D, Lapouble E, Freneaux P, Champigneulle J, Bouvier R, Walder D, Ambros IM, Hutter C, Sorz E, Amaral AT, de Álava E, Schallmoser K, Strunk D, Rinner B, Liegl-Atzwanger B, Huppertz B, Leithner A, de Pinieux G, Terrier P, Laurence V, Michon J, Ladenstein R, Holter W, Windhager R, Dirksen U, Ambros PF, Delattre O, Kovar H, Bock C, Tomazou EM. (2017 Mar 23)
DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma.
Nature Médecine- : DOI : 10.1038/nm.4273

Résumé

Developmental tumors in children and young adults carry few genetic alterations, yet they have diverse clinical presentation. Focusing on Ewingsarcoma, we sought to establish the prevalence and characteristics of epigenetic heterogeneityin genetically homogeneous cancers. We performed genome-scale DNAmethylationsequencing for a large cohort of Ewingsarcomatumors and analyzed epigenetic heterogeneityon three levels: between cancers, between tumors, and within tumors. We observed consistent DNAhypomethylation at enhancers regulated by the disease-defining EWS-FLI1 fusion protein, thus establishing epigenomic enhancer reprogramming as a ubiquitous and characteristic feature of Ewingsarcoma. DNAmethylationdifferences between tumors identified a continuous diseasespectrumunderlying Ewingsarcoma, which reflected the strength of an EWS-FLI1 regulatory signature and a continuum between mesenchymal and stem cell signatures. There was substantial epigenetic heterogeneitywithin tumors, particularly in patients with metastatic disease. In summary, our study provides a comprehensive assessment of epigenetic heterogeneityin Ewingsarcomaand thereby highlights the importance of considering nongenetic aspects of tumor heterogeneityin the context of cancer biology and personalized medicine.

, Philip C Haycock, Stephen Burgess, Aayah Nounu, Jie Zheng, George N Okoli, Jack Bowden, Kaitlin Hazel Wade, Nicholas J Timpson, David M Evans, Peter Willeit, Abraham Aviv, Tom R Gaunt, Gibran Hemani, Massimo Mangino, Hayley Patricia Ellis, Kathreena M Kurian, Karen A Pooley, Rosalind A Eeles, Jeffrey E Lee, Shenying Fang, Wei V Chen, Matthew H Law, Lisa M Bowdler, Mark M Iles, Qiong Yang, Bradford B Worrall, Hugh Stephen Markus, Rayjean J Hung, Chris I Amos, Amanda B Spurdle, Deborah J Thompson, Tracy A O'Mara, Brian Wolpin, Laufey Amundadottir, Rachael Stolzenberg-Solomon, Antonia Trichopoulou, N Charlotte Onland-Moret, Eiliv Lund, Eric J Duell, Federico Canzian, Gianluca Severi, Kim Overvad, Marc J Gunter, Rosario Tumino, Ulrika Svenson, Andre van Rij, Annette F Baas, Matthew J Bown, Nilesh J Samani, Femke N G van t'Hof, Gerard Tromp, Gregory T Jones, Helena Kuivaniemi, James R Elmore, Mattias Johansson, James Mckay, Ghislaine Scelo, Robert Carreras-Torres, Valerie Gaborieau, Paul Brennan, Paige M Bracci, Rachel E Neale, Sara H Olson, Steven Gallinger, Donghui Li, Gloria M Petersen, Harvey A Risch, Alison P Klein, Jiali Han, Christian C Abnet, Neal D Freedman, Philip R Taylor, John M Maris, Katja K Aben, Lambertus A Kiemeney, Sita H Vermeulen, John K Wiencke, Kyle M Walsh, Margaret Wrensch, Terri Rice, Clare Turnbull, Kevin Litchfield, Lavinia Paternoster, Marie Standl, Gonçalo R Abecasis, John Paul SanGiovanni, Yong Li, Vladan Mijatovic, Yadav Sapkota, Siew-Kee Low, Krina T Zondervan, Grant W Montgomery, Dale R Nyholt, David A van Heel, Karen Hunt, Dan E Arking, Foram N Ashar, Nona Sotoodehnia, Daniel Woo, Jonathan Rosand, Mary E Comeau, W Mark Brown, Edwin K Silverman, John E Hokanson, Michael H Cho, Jennie Hui, Manuel A Ferreira, Philip J Thompson, Alanna C Morrison, Janine F Felix, Nicholas L Smith, Angela M Christiano, Lynn Petukhova, Regina C Betz, Xing Fan, Xuejun Zhang, Caihong Zhu, Carl D Langefeld, Susan D Thompson, Feijie Wang, Xu Lin, David A Schwartz, Tasha Fingerlin, Jerome I Rotter, Mary Frances Cotch, Richard A Jensen, Matthias Munz, Henrik Dommisch, Arne S Schaefer, Fang Han, Hanna M Ollila, Ryan P Hillary, Omar Albagha, Stuart H Ralston, Chenjie Zeng, Wei Zheng, Xiao-Ou Shu, Andre Reis, Steffen Uebe, Ulrike Hüffmeier, Yoshiya Kawamura, Takeshi Otowa, Tsukasa Sasaki, Martin Lloyd Hibberd, Sonia Davila, Gang Xie, Katherine Siminovitch, Jin-Xin Bei, Yi-Xin Zeng, Asta Försti, Bowang Chen, Stefano Landi, Andre Franke, Annegret Fischer, David Ellinghaus, Carlos Flores, Imre Noth, Shwu-Fan Ma, Jia Nee Foo, Jianjun Liu, Jong-Won Kim, David G Cox, Olivier Delattre, Olivier Mirabeau, Christine F Skibola, Clara S Tang, Merce Garcia-Barcelo, Kai-Ping Chang, Wen-Hui Su, Yu-Sun Chang, Nicholas G Martin, Scott Gordon, Tracey D Wade, Chaeyoung Lee, Michiaki Kubo, Pei-Chieng Cha, Yusuke Nakamura, Daniel Levy, Masayuki Kimura, Shih-Jen Hwang, Steven Hunt, Tim Spector, Nicole Soranzo, Ani W Manichaikul, R Graham Barr, Bratati Kahali, Elizabeth Speliotes, Laura M Yerges-Armstrong, Ching-Yu Cheng, Jost B Jonas, Tien Yin Wong, Isabella Fogh, Kuang Lin, John F Powell, Kenneth Rice, Caroline L Relton, Richard M Martin, George Davey Smith (2017 Feb 28)
Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study.
JAMA oncology : DOI : 10.1001/jamaoncol.2016.5945

Résumé

The causal direction and magnitude of the association between telomere length and incidence of cancer and non-neoplastic diseases is uncertain owing to the susceptibility of observational studies to confounding and reverse causation.

Nathan C Sheffield, Gaelle Pierron, Johanna Klughammer, Paul Datlinger, Andreas Schönegger, Michael Schuster, Johanna Hadler, Didier Surdez, Delphine Guillemot, Eve Lapouble, Paul Freneaux, Jacqueline Champigneulle, Raymonde Bouvier, Diana Walder, Ingeborg M Ambros, Caroline Hutter, Eva Sorz, Ana T Amaral, Enrique de Álava, Katharina Schallmoser, Dirk Strunk, Beate Rinner, Bernadette Liegl-Atzwanger, Berthold Huppertz, Andreas Leithner, Gonzague de Pinieux, Philippe Terrier, Valérie Laurence, Jean Michon, Ruth Ladenstein, Wolfgang Holter, Reinhard Windhager, Uta Dirksen, Peter F Ambros, Olivier Delattre, Heinrich Kovar, Christoph Bock, Eleni M Tomazou (2017 Jan 31)
DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma.
Nature medicine : DOI : 10.1038/nm.4273

Résumé

Developmental tumors in children and young adults carry few genetic alterations, yet they have diverse clinical presentation. Focusing on Ewing sarcoma, we sought to establish the prevalence and characteristics of epigenetic heterogeneity in genetically homogeneous cancers. We performed genome-scale DNA methylation sequencing for a large cohort of Ewing sarcoma tumors and analyzed epigenetic heterogeneity on three levels: between cancers, between tumors, and within tumors. We observed consistent DNA hypomethylation at enhancers regulated by the disease-defining EWS-FLI1 fusion protein, thus establishing epigenomic enhancer reprogramming as a ubiquitous and characteristic feature of Ewing sarcoma. DNA methylation differences between tumors identified a continuous disease spectrum underlying Ewing sarcoma, which reflected the strength of an EWS-FLI1 regulatory signature and a continuum between mesenchymal and stem cell signatures. There was substantial epigenetic heterogeneity within tumors, particularly in patients with metastatic disease. In summary, our study provides a comprehensive assessment of epigenetic heterogeneity in Ewing sarcoma and thereby highlights the importance of considering nongenetic aspects of tumor heterogeneity in the context of cancer biology and personalized medicine.

G-A Franzetti, K Laud-Duval, W van der Ent, A Brisac, M Irondelle, S Aubert, U Dirksen, C Bouvier, G de Pinieux, E Snaar-Jagalska, P Chavrier, O Delattre (2017 Jan 31)
Cell-to-cell heterogeneity of EWSR1-FLI1 activity determines proliferation/migration choices in Ewing sarcoma cells.
Oncogene : DOI : 10.1038/onc.2016.498

Résumé

Ewing sarcoma is characterized by the expression of the chimeric EWSR1-FLI1 transcription factor. Proteomic analyses indicate that the decrease of EWSR1-FLI1 expression leads to major changes in effectors of the dynamics of the actin cytoskeleton and the adhesion processes with a shift from cell-to-cell to cell-matrix adhesion. These changes are associated with a dramatic increase of in vivo cell migration and invasion potential. Importantly, EWSR1-FLI1 expression, evaluated by single-cell RT-ddPCR/immunofluorescence analyses, and activity, assessed by expression of EWSR1-FLI1 downstream targets, are heterogeneous in cell lines and in tumours and can fluctuate along time in a fully reversible process between EWSR1-FLI1(high) states, characterized by highly active cell proliferation, and EWSR1-FLI1(low) states where cells have a strong propensity to migrate, invade and metastasize. This new model of phenotypic plasticity proposes that the dynamic fluctuation of the expression level of a dominant oncogene is an intrinsic characteristic of its oncogenic potential.Oncogene advance online publication, 30 January 2017; doi:10.1038/onc.2016.498.

A Bertrand, C Rondenet, J Masliah-Planchon, P Leblond, A de la Fourchardière, D Pissaloux, K Aït-Raïs, D Lequin, A Jouvet, P Freneaux, H Sevestre, D Ranchere-Vince, A Tauziede-Espariat, C-A Maurage, K Silva, G Pierron, O Delattre, P Varlet, D Frappaz, F Bourdeaut (2017 Jan 6)

Rhabdoid component emerging as a subclonal evolution of paediatric glioneuronal tumours.

Neuropathology and applied neurobiology : DOI : 10.1111/nan.12379

Résumé

Atypical teratoid/rhabdoid tumors (AT/RT) are high-grade tumors partially composed of rhabdoid cells (1). The 1-year overall survival rate is 41% (2). Rhabdoid cells have large eccentric nuclei, a single prominent nucleolus, and abundant cytoplasm with eosinophilic inclusions. The immunohistochemical profile of these cells frequently includes loss of nuclear BAF47 expression due to loss of the SMARCB1 locus combined with a mutation of the other allele (3). This article is protected by copyright. All rights reserved.

Gudrun Schleiermacher, Olivier Delattre (2017 Jan 2)

Kids Enter the MATCH.

Journal of the National Cancer Institute : DOI : djw305

Résumé

Année de publication : 2016

Edoardo Missiaglia, Chris J Shepherd, Ewa Aladowicz, David Olmos, Joanna Selfe, Gaëlle Pierron, Olivier Delattre, Zoe Walters, Janet Shipley (2016 Dec 17)

MicroRNA and gene co-expression networks characterize biological and clinical behavior of rhabdomyosarcomas.
Cancer letters : DOI : S0304-3835(16)30623-1

Résumé

Rhabdomyosarcomas (RMS) in children and adolescents are heterogeneous sarcomas broadly defined by skeletal muscle features and the presence/absence of PAX3/7-FOXO1 fusion genes. MicroRNAs are small non-coding RNAs that regulate gene expression in a cell context specific manner. Sequencing analyses of microRNAs in 64 RMS revealed expression patterns separating skeletal muscle, fusion gene positive and negative RMS. Integration with parallel gene expression data assigned biological functions to 12 co-expression networks/modules that reassuringly included myogenic roles strongly correlated with microRNAs known in myogenesis and RMS development. Modules also correlated with clinical outcome and fusion status. Regulation of microRNAs by the fusion protein was demonstrated after PAX3-FOXO1 reduction, exemplified by miR-9-5p. MiR-9-5p levels correlated with poor outcome, even within fusion gene positive RMS, and were higher in metastatic versus non-metastatic disease. MiR-9-5p reduction inhibited RMS cell migration. Our findings reveal microRNAs in a regulatory framework of biological and clinical significance in RMS.

Thomas Pincez, Nathalie Clément, Eve Lapouble, Gaëlle Pierron, Maud Kamal, Ivan Bieche, Virginie Bernard, Paul Fréneaux, Jean Michon, Daniel Orbach, Isabelle Aerts, Hélène Pacquement, Franck Bourdeaut, Irene Jiménez, Estelle Thébaud, Caroline Oudot, Cécile Vérité, Sophie Taque, Cormac Owens, François Doz, Christophe Le Tourneau, Olivier Delattre, Gudrun Schleiermacher (2016 Nov 30)
Feasibility and clinical integration of molecular profiling for target identification in pediatric solid tumors.
Pediatric blood & cancer : DOI : 10.1002/pbc.26365

Résumé

The role of tumor molecular profiling in directing targeted therapy utilization remains to be defined for pediatric tumors. We aimed to evaluate the feasibility of a sequencing and molecular biology tumor board (MBB) program, and its clinical impact on children with solid tumors.

Tao He, Didier Surdez, Juha K Rantala, Saija Haapa-Paananen, Jozef Ban, Maximilian Kauer, Eleni Tomazou, Vidal Fey, Javier Alonso, Heinrich Kovar, Olivier Delattre, Kristiina Iljin (2016 Oct 30)
High-throughput RNAi screen in Ewing sarcoma cells identifies leucine rich repeats and WD repeat domain containing 1 (LRWD1) as a regulator of EWS-FLI1 driven cell viability.
Gene : 137-146 : DOI : S0378-1119(16)30827-7

Résumé

A translocation leading to the formation of an oncogenic EWS-ETS fusion protein defines Ewing sarcoma. The most frequent gene fusion, present in 85 percent of Ewing sarcomas, is EWS-FLI1. Here, a high-throughput RNA interference screen was performed to identify genes whose function is critical for EWS-FLI1 driven cell viability. In total, 6781 genes were targeted by siRNA molecules and the screen was performed both in presence and absence of doxycycline-inducible expression of the EWS-FLI1 shRNA in A673/TR/shEF Ewing sarcoma cells. The Leucine rich repeats and WD repeat Domain containing 1 (LRWD1) targeting siRNA pool was the strongest hit reducing cell viability only in EWS-FLI1 expressing Ewing sarcoma cells. LRWD1 had been previously described as a testis specific gene with only limited information on its function. Analysis of LRWD1 mRNA levels in patient samples indicated that high expression associated with poor overall survival in Ewing sarcoma. Gene ontology analysis of LRWD1 co-expressed genes in Ewing tumors revealed association with DNA replication and analysis of differentially expressed genes in LRWD1 depleted Ewing sarcoma cells indicated a role in connective tissue development and cellular morphogenesis. Moreover, EWS-FLI1 repressed genes with repressive H3K27me3 chromatin marks were highly enriched among LRWD1 target genes in A673/TR/shEF Ewing sarcoma cells, suggesting that LRWD1 contributes to EWS-FLI1 driven transcriptional regulation. Taken together, we have identified LRWD1 as a novel regulator of EWS-FLI1 driven cell viability in A673/TR/shEF Ewing sarcoma cells, shown association between high LRWD1 mRNA expression and aggressive disease and identified processes by which LRWD1 may promote oncogenesis in Ewing sarcoma.