Supplemental Data

Supplemental Tables and Figures

Global Profiling of the Cellular Alternative RNA Splicing Landscape During Virus-host Interactions

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| Table A. RNA-sequencing data | | | | | |
|------------------------------|-----------------|-------------|--|--|--|
| Sample | Number of bases | HiSeq Reads | | | |
| Mock 1 | 9 270 066 200 | 46 350 331 | | | |
| Mock 2 | 9 400 946 800 | 47 004 734 | | | |
| Mock 3 | 7 880 753 600 | 39 403 768 | | | |
| Reovirus 1 | 10 499 367 400 | 52 496 837 | | | |
| Reovirus 2 | 10 352 922 800 | 51 764 614 | | | |
| Reovirus 3 | 8 850 997 600 | 44 254 988 | | | |

RNA-seq was performed on uninfected (mock-infected) cells, and cells infected with reovirus

(14 hours post-infection). Sequencing was done in triplicate.

Table B. Distribution of ΔPSI values in the 240 differentially spliced ASEs

| ΔΡSI | Number of ASEs modified |
|-----------|----------------------------|
| [-80,-70[| 1 |
| [-70,-60[| 0 |
| [-60,-50[| 4 |
| [-50,-40[| 4 |
| [-40,-30[| 15 |
| [-30,-20[| 35 |
| [-20,-10[| 60 |
|]10,20] | 64 |
|]20,30] | 39 |
|]30,40] | 11 |
|]40,50] | 3 |
|]50,60] | 2 |
|]60,70] | 2 |

| Table C: Seq | uencing results (Sa | nger) for splicing | junctions confirme | ed by RT-PCR |
|------------------------------|---------------------|--------------------|--|--|
| Gene | ASE Form | Splicing junction | Predicted sequence | Sequencing results |
| II34 Exon 5 Exon 6 Exon 7 | Short | 5-7 | CAGCGGAGCCT CATGGATGTGG AGATTGGC | CAGCGGAGCCT CATGGATGTGG AGATTGGC |
| | Long | 5-6 | NA | NA |
| | Long | 6-7 | NA | NA |
| hnRNPA2B1 | Short | 8-10 | GAGGAGGACCT GGAGGAAATTA TGGAAGTG | GAGGAGGACCT GGAGGAAATTA TGGAAGTG |
| | Long | 8-9 | GAGGAGGACCT GGAGGTGGCAA TTTTGGAG | GAGGAGGACCT GGAGGTGGCAA TTTTGGAG |
| | Long | 9-10 | ACAACTATGGA GGAGGAAATTA TGGAAGTG | ACAACTATGGA GGAGGAAATTA TGGAAGTG |

NA: Splicing junction expressed at levels too low to allow sequencing

| Table D. Bioinformatic prediction of functional changes caused by some identified ASEs | | | | | |
|--|---------------|---|---|--|--|
| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
| Abi1 | -50.8 | exon- cassette+alternate- 3p+multiple-exon- cassette | abl-interactor 1 | -29 | Unknown |
| Adar | -25.1 | alternate-5p | adenosine deaminase, RNA- specific | -26 | Unknown |
| Agfg1 | -27.6 | alternate-3p | ArfGAP with FG repeats 1 | -19 | Unknown |
| Apol9a | 22.9 | alternate-5p | apolipoprotein L 9a | 0 | No predicted functional change |
| Arhgap11a | -42.9 | exon- cassette+alternate- 3p+intron-retention | Rho GTPase activating protein 11A | -515 | NLS and RhoGAP domain loss in short isoform |
| Arhgap11a | 16.7 | exon- cassette+alternate- 3p+intron-retention | Rho GTPase activating protein 11A | -489 | Premature stop codon introduced by intron retention in long isoform |
| Asph | 13.8 | exon-cassette | aspartate-beta- hydroxylase | 83 | Unknown |
| Atat1 | 13.8 | exon-cassette | alpha tubulin acetyltransferase 1 | 23 | Unknown |
| Atxn7l1 | -22.4 | exon-cassette | ataxin 7-like 1 | -51 | Unknown |
| Bnip2 | -18.3 | exon-cassette | BCL2/adenovirus E1B interacting protein 2 | -6 | Unknown |
| Bora | 37.5 | exon-cassette | bora, aurora kinase A activator | -251 | Premature stop codon in long isoform |
| Bptf | -22.9 | alternate-5p | bromodomain PHD finger transcription factor | -281 | Unknown |
| Calu | 13.3 | mutually-exclusive- exon | Calumenin | 0 | Unknown |
| Cbwd1 | -23.1 | alternate-5p | COBW domain containing 1 | -121 | CobW/HypB/UreG domain truncated in short isoform |
| Ccdc136 | -10.2 | exon-cassette | coiled-coil domain containing 136 | -47 | Unknown |
| Ccdc15 | 14.8 | alternate-5p | coiled-coil domain containing 15 | 116 | Unknown |
| Cdkn2aip | -18.2 | alternate-5p | CDKN2A interacting protein | -444 | Premature stop codon inducing a NLS loss in short isoform |
| Celf1 | 11.2 | alternate-3p | CUGBP, Elav-like family member 1 | 1 | Unknown |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|---------|---------------|---|---|--|---|
| Cflar | -14.8 | exon-cassette | CASP8 and FADD- like apoptosis regulator | -186 | Loss of the two DED domains in short isoform |
| Cflar | 27.6 | exon-cassette | CASP8 and FADD- like apoptosis regulator | -186 | Loss of the two DED domains in long isoform |
| Clip1 | -18.9 | alternate-5p | CAP-GLY domain containing linker protein 1 | -76 | Unknown |
| Clk4 | 11.9 | exon- cassette+intron- retention | CDC like kinase 4 | 180 | Gain of 10 NLS and full-length Pkinase domain in long isoform |
| Cwc22 | 21.5 | alternate-5p | CWC22 spliceosome- associated protein homolog (S, cerevisiae) | -6 | Unknown |
| Cwc22 | 19.9 | exon-cassette | CWC22 spliceosome- associated protein homolog (S, cerevisiae) | 6 | Unknown |
| E2f3 | -20.9 | alternate-3p | E2F transcription factor 3 | -6 | Additionnal NLS in short isoform |
| Edc3 | -26.5 | exon-cassette | enhancer of mRNA decapping 3 homolog (S, cerevisiae) | -183 | Loss of Edc3- linker domain, LSM14 domain and truncation of YjwF_N domain in short isoform |
| Eif4a2 | -11.4 | exon-cassette | eukaryotic translation initiation factor 4A2 | -95 | Truncation of DEAD box helicase domain in short isoform |
| Eif4h | -16.7 | exon-cassette | eukaryotic translation initiation factor 4H | -20 | Unknown |
| Erbb2ip | -30.0 | exon- cassette+alternate- 3p+multiple-exon- cassette+mutually- exclusive-exon | Erbb2 interacting protein | -39 | Unknown |
| Erbb2ip | 23.3 | exon- cassette+alternate- 3p+multiple-exon- cassette+mutually- exclusive-exon | Erbb2 interacting protein | -384 | Premature stop codon, C-Term PDZ domain loss in short isoform |
| Fam179b | -30.2 | exon-cassette | family with sequence similarity 179. member B | -50 | Unknown |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|-----------|---------------|---|--|--|---|
| Flcn | 35.8 | alternate-3p | folliculin | -129 | Premature stop codon, resulting in Folliculin domain truncation (174AA, C-term) |
| Foxk2 | -29.7 | exon-cassette | forkhead box K2 | -401 | Unknown |
| G2e3 | -53.0 | exon- cassette+alternate- 3p+multiple-exon- cassette | G2/M-phase specific E3 ubiquitin ligase | 116 | Unknown |
| Gdap2 | 15.1 | alternate-3p | ganglioside- induced differentiation- associated-protein 2 | 256 | Complete CRAL and TRIO domains in long isoform |
| Gen1 | -28.7 | exon-cassette | Gen homolog 1, endonuclease (Drosophila) | -10 | Earlier start codon in long isoform; Short isoform loses its XPG_N domain in N-term |
| Gls | 11.3 | alternate-3p | glutaminase | -376 | Unknown |
| Gpbp1 | 25.6 | exon-cassette | GC-rich promoter binding protein 1 | 20 | Unknown |
| Hmga1 | 15.6 | exon- cassette+alternate- 5p+intron-retention | high mobility group AT-hook 1 | 0 | 5'UTR sequence change |
| Hnrnpa2b1 | -13.6 | exon-cassette | heterogeneous nuclear ribonucleoprotein A2/B1 | -40 | Additionnal HnRNPA1 domain in N-term of short isoform |
| 1134 | 58.9 | exon-cassette | interleukin 34 | -16 | Frameshift introducing a premature stop codon in exon 8; truncation of II34 domain |
| lif3 | 13.2 | exon-cassette | interleukin enhancer binding factor 3 | 13 | Unknown |
| lqce | 17.6 | exon-cassette | IQ motif containing E | 17 | Unknown |
| lqce | -19.2 | exon-cassette | IQ motif containing E | -17 | Unknown |
| lvns1abp | 30.8 | exon- cassette+alternate- 3p | influenza virus NS1A binding protein | -281 | NLS and BTB domains loss in |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|---------|---------------|------------------------------------|---|--|---|
| Kat5 | 28.7 | exon-cassette | K(lysine) acetyltransferase 5 | 52 | Long isoform have two NLS instead of only one in the short isoform |
| Kat6a | -13.6 | exon-cassette | K(lysine) acetyltransferase 6A | 130 | Unknown |
| Kmt2e | 10.8 | exon-cassette | lysine (K)-specific methyltransferase 2E | -1602 | Loss of 6 NLS and SET and PHD domains in long isoform |
| Lrrfip1 | 13.1 | exon-cassette | leucine rich repeat (in FLII) interacting protein 1 | 24 | Truncation in double-stranded RNA binding protein DUF2051 in long isoform |
| Macf1 | -25.2 | multiple-exon- cassette | microtubule-actin crosslinking factor 1 | -2027 | Loss of all 9 Plectin repeat domains in short isoform |
| Matr3 | 12.3 | alternate-5p | matrin 3 | 0 | No predicted functional change |
| Мах | 11.3 | exon-cassette | Max protein | -122 | NLS and Helix- Loop-Helix domain loss in long isoform |
| Mbnl2 | 24.1 | exon-cassette | muscleblind-like 2 | 18 | Unknown |
| Mdm2 | -58.8 | exon- cassette+alternate- 5p | transformed mouse 3T3 cell double minute 2 | -197 | SWIB domain in N-Term loss in short isoform |
| Mon2 | 38.3 | exon-cassette | MON2 homolog (yeast) | 7 | 6 residue gap in Mon2 domain in short isoform |
| Morn1 | -16.3 | alternate-5p | MORN repeat containing 1 | -245 | Loss of 4 MORN domain out of 8 in short isoform |
| Msh4 | -38.7 | alternate-5p | mutS homolog 4 (E, coli) | 404 | Premature stop codon in long isoform |
| Mtif3 | 25.0 | exon- cassette+alternate- 5p | mitochondrial translational initiation factor 3 | 0 | Unknown |
| Nabp1 | 41.4 | alternate-5p+intron- retention | nucleic acid binding protein 1 | -91 | Unknown |
| Naip2 | 21.8 | exon-cassette | NLR family, apoptosis inhibitory protein 2 | 56 | Unknown |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|---------|---------------|--|--|--|---|
| Nasp | -16.5 | exon-cassette | nuclear autoantigenic sperm protein (histone-binding) | -325 | Unknown |
| Nde1 | -16.6 | alternate-3p | nuclear distribution gene E homolog 1 (A nidulans) | 27 | Unknown |
| Nek1 | 26.9 | exon-cassette | NIMA (never in mitosis gene a)- related expressed kinase 1 | 29 | Unknown |
| Neurl4 | -19.2 | exon-cassette | neuralized homolog 4 (Drosophila) | -22 | Unknown |
| Nfx1 | 28.3 | alternate-3p | nuclear transcription factor, X-box binding 1 | -14 | Unknown |
| Odf2I | -16.0 | exon-cassette | outer dense fiber of sperm tails 2-like | -96 | Unknown |
| Opa1 | -14.5 | exon-cassette | optic atrophy 1 | -37 | Unknown |
| Pan3 | 17.4 | exon-cassette | PAN3 polyA specific ribonuclease subunit homolog (S. cerevisiae) | 258 | Unknown |
| Pcgf5 | 15.5 | exon-cassette | polycomb group ring finger 5 | 20 | C-term RAWUL domain truncated in long isoform |
| Phactr4 | -16.8 | exon-cassette | phosphatase and actin regulator 4 | -27 | RPEL repeat domain loss in short isoform |
| Piga | -33.8 | alternate-5p | phosphatidylinositol glycan anchor biosynthesis, class A | -316 | PIGA domain loss in short isoform |
| Pitpnb | -21.8 | exon-cassette | phosphatidylinositol transfer protein, beta | -1 | Unknown |
| Pnpla7 | 69.1 | alternate-5p | patatin-like phospholipase domain containing 7 | -886, -52, - 454 or +380 | Unknown |
| Polg2 | -13.5 | alternate-5p | polymerase (DNA directed), gamma 2, accessory subunit | -44 | Unknown |
| Ppfibp1 | -16.1 | exon- cassette+intron- retention | PTPRF interacting protein, binding protein 1 (liprin beta 1) | -11 | Unknown |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|----------|---------------|--|---|--|--|
| Ppp1r12a | 10.2 | exon-cassette | protein phosphatase 1, regulatory (inhibitor) subunit 12A | 422 | Unknown |
| Pqlc1 | 50.9 | exon-cassette | PQ loop repeat containing 1 | 18 | Unknown |
| Prpf39 | 18.5 | exon- cassette+multiple- exon-cassette | PRP39 pre-mRNA processing factor 39 homolog (yeast) | -201, -239 | Loss of part of Tetratricopeptide- like helical domain and HAT reapeats in both C- and N- term |
| Pum2 | -11.2 | exon-cassette | pumilio RNA- binding family member 2 | -79 | Unknown |
| Ranbp3 | -27.0 | exon- cassette+multiple- exon-cassette | RAN binding protein 3 | 331 | NLS loss and full RanBP1 domain in long isoform |
| Rfx5 | 34.7 | exon- cassette+alternate- 5p | regulatory factor X, 5 (influences HLA class II expression) | 185 | NLS gain and full- length RFX5 DNA-binding domain in long isoform |
| Rnf135 | -31.1 | exon-cassette | ring finger protein 135 | -216 | Zinc finger of C3HC4-type domain loss in short isoform |
| Rnps1 | -25.7 | exon- cassette+multiple- exon-cassette | ribonucleic acid binding protein S1 | -23 | Unknown |
| Rnps1 | -14.6 | exon- cassette+multiple- exon-cassette | ribonucleic acid binding protein S1 | -23 | Unknown |
| Scaf11 | -11.6 | alternate-5p | SR-related CTD- associated factor 11 | -16 | Unknown |
| Senp1 | 22.9 | exon-cassette | SUMO1/sentrin specific peptidase 1 | -142 | Unknown |
| Sfswap | -24.8 | alternate-5p | splicing factor, suppressor of white-apricot family | -724 | 47 AA truncation in Alternative splicing regulator domain and 2 Surp module domain loss in short isoform |
| Skil | -14.2 | alternate-5n | SKI-like | -35 | Unknown |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔΑΑ) | Predicted functional consequence |
|----------|---------------|---|---|--|---|
| SIc23a2 | -12.2 | alternate-3p | solute carrier family 23 (nucleobase transporters), member 2 | -308 | 208 AA loss in the N-term of Xan_ur_permease domain in short isoform |
| Son | 25.7 | exon- cassette+alternate- 5p | Son DNA binding protein | -2198 | Premature stop codon in long isoform, introducing 4 NLS and G-patch, Arginine/Serine- Rich protein 1 and double-stranded RNA binding domain loss |
| Spef2 | 18.4 | exon-cassette | sperm flagellar 2 | 923 | Unknown |
| Spopl | 27.8 | exon-cassette | speckle-type POZ protein-like | 56 | Unknown |
| Stx3 | 39.5 | exon- cassette+mutually- exclusive-exon | syntaxin 3 | 97 | 75 AA truncation of Syntaxin domain in long isoform |
| Тbр | -44.3 | exon-cassette | TATA box binding protein | -56 | TBP domain loss and truncation of first TBP domain's end in short isoform |
| Tcf12 | 30.7 | exon- cassette+intron- retention | transcription factor 12 | 24 | Unknown |
| Tmem132a | 66.1 | alternate-3p | transmembrane protein 132A | 29 | Unknown |
| Tmem168 | -32.5 | exon-cassette | transmembrane protein 168 | -384 | Unknown |
| Tmem19 | -15.0 | alternate-5p | transmembrane protein 19 | 12 | Full lenght DUF92 integral membrane domain in long isoform |
| Ттро | -38.3 | exon- cassette+multiple- exon-cassette | thymopoietin | -40 | Unknown |
| Ттро | -11.5 | exon- cassette+multiple- exon-cassette | thymopoietin | -72 | Unknown |
| Tpp2 | 10.7 | exon-cassette | tripeptidyl peptidase II | -130 | Unknown |
| Tra2a | 21.2 | exon-cassette | transformer 2 alpha homolog (Drosophila) | 97 | Full-length RNA recognition motif in long isoform |

| Gene | Delta- PSI | Event Type | Full name | Predicted residue variation caused by alternative splicing modification (ΔAA) | Predicted functional consequence |
|---------------|---------------|---|---|--|---|
| Trappc13 | -29.9 | exon-cassette | trafficking protein particle complex 13 | -6 | DUF974 domain truncation of 6 AA in short isoform |
| Ubap1 | -21.4 | exon-cassette | ubiquitin- associated protein 1 | -61 | Unknown |
| Ubr3 | 11.3 | alternate-3p | ubiquitin protein ligase E3 component n- recognin 3 | 4 | Unknown |
| Upf1 | -23.4 | alternate-5p | UPF1 regulator of nonsense transcripts homolog (yeast) | -11 | Unknown |
| Wsb1 | 19.9 | alternate-3p | WD repeat and SOCS box- containing 1 | -177 | Premature stop codon in long isoform, resulting in a truncated protein containing only a WD, G-beta domain instead of 4 WD, G-beta domain and a SOCS box domain |
| Xdh | -25.6 | alternate-5p | xanthine dehydrogenase | -599 | NLS appearance in short isoform |
| Zfp207 | -12.5 | exon-cassette | zinc finger protein 207 | -6 | Unknown |
| Zfp788 | -32.4 | exon- cassette+alternate- 3p+multiple-exon- cassette | zinc finger protein 788 | -532 | Unknown |
| Zmynd11 | -17.1 | exon-cassette | zinc finger, MYND domain containing 11 | -54 | Unknown |
| Zyx | 13.8 | exon-cassette | zyxin | 31 | Unknown |
| 1700057G04Rik | -31.1 | exon-cassette | RIKEN cDNA 1700057G04 gene | -76 | Truncation in Scramblase domain in short isoform |
| 2310057M21Rik | -15.9 | alternate-5p | RIKEN cDNA 2310057M21 gene | 77 | Unknown |
| 4631405J19Rik | -45.7 | alternate-3p | RIKEN cDNA 4631405J19 gene | -100 | Unknown |
| 4930511M06Rik | -23.6 | exon-cassette | RIKEN cDNA 4930511M06 gene | NA | Non-coding RNA |

Figure A. Detection of reovirus genes in infected cells by qRT-PCR.

(A) Total RNA was extracted from both uninfected and infected cells (14 h post-infection). Viral infection was confirmed by qRT-PCR using specific primers for three viral genes (M1, S1, L1). A control reaction without template (NTC: no template control) was also performed. All three viral genes were detected in the infected cells samples but were undetectable in the uninfected (mock) samples (absence of amplification or nonspecific amplification). Cq: quantification cycle.

(B) Primers used for qPCR detection.



qRT-PCR data on amplification of viral genes in uninfected (mock) and infected cells

| Orthoreovirus Primer | Cq Mock | Cq infected | Cq NTC | Color |
|-------------------------|------------|----------------|------------|-------|
| L1_1 | Undetected | 20.52 | Undetected | Black |
| L1_2 | Undetected | 19.22 | Undetected | |
| M1_1 | Undetected | 18.57 | Undetected | Pink |
| M1_2 | Undetected | 19.68 | Undetected | Green |
| S1_1 | Undetected | 16.93 | Undetected | Blue |
| S1_2 | Undetected | 17.00 | Undetected | Gray |

| - |
|---|
| |
| |

| Primers design for qRT-PCR amplification of reovirus genes | | | | |
|--|-----------------------------|----------------------|-----------------------------|----------------------|
| Name | Primer forward | Sequence | Primer reverse | Sequence |
| L1_1 | orthoreovirus_t3d_seg_L1.F1 | GGCAAAGACGGTGTCGGGTC | orthoreovirus_t3d_seg_L1.R1 | TGCGTCCGCTTCTGACTCCT |
| L1_2 | orthoreovirus_t3d_seg_L1.F2 | CTAGGGGTGGATCTGGCGCA | orthoreovirus_t3d_seg_L1.R2 | TCGCTAATTGTGCCGCCTGG |
| M1_1 | orthoreovirus_t3d_seg_M1.F1 | AGCGCGCAGCCTAAATGGTT | orthoreovirus_t3d_seg_M1.R1 | ACGTAGATGCCGGGTCTGCT |
| M1_2 | orthoreovirus_t3d_seg_M1.F2 | AGATGAGGCTTTCGTGCGGC | orthoreovirus_t3d_seg_M1.R2 | GCATGTCACGGATCACGCCA |
| S1_1 | orthoreovirus_t3d_seg_S1.F1 | GGTCGGATGGATCCTCGCCT | orthoreovirus_t3d_seg_S1.R1 | TCGAGTCCCTGGGTGATCCG |
| S1_2 | orthoreovirus_t3d_seg_S1.F2 | CCTCCGGATCACCCAGGGAC | orthoreovirus_t3d_seg_S1.R2 | TGTCCCACTCGAGCACCCAA |

Figure B. Heatmap representation of gene expression of total cellular genes in both infected and uninfected (mock) cells.

RNA sequencing was done in triplicate for each condition. The map represents the number of transcripts sequences (TPM: transcripts per million) in a color-coded logarithmic scale. Blue and green indicates high levels of gene expression while yellow indicates low levels of gene expression.



Figure C. List of the 570 genes for which the expression was the most significantly modified following viral infection. The list of genes is shown with the corresponding expression profile of each gene. The level of gene expression is presented on a logarithmic scale (Log_2)

Gene

Expression change (Log₂)

| | - | 11 |
|---------------|---|----|
| MX1 | | |
| RSAD2 | | |
| IFIT1 | | |
| GM14446 | | |
| BC023105 | | |
| 1830012O16RIK | | |
| DDX60 | | |
| MX2 | | |
| OASL2 | | |
| ZBP1 | | |
| IFIT3 | | |
| GBP3 | | |
| CXCL10 | | |
| GM12250 | | |
| TGTP1 | | |
| GBP7 | | |
| IFI205 | | |
| IF144 | | |
| GBP2B | | |
| IFI44L | | |
| USP18 | | |
| M55219 | | |
| GBP2 | | |
| CXCL11 | | |
| BANK1 | | |
| PYDC3 | | |
| GBP5 | | |
| RTP4 | | |
| BC094916 | | |
| OASL1 | | |
| PHF11A | | |
| BC038927 | | |
| XAF1 | | |
| IRGM2 | | |
| PYHIN1 | | |
| PHF11B | | |
| IGTP | | |
| OLFR56 | | |

Figure C

Gene

Expression change (Log₂)

| ۲ ۲ | - | 7 |
|---------------|---|---|
| AKT3 | | |
| IRF7 | | |
| CXCL9 | | |
| PHF11D | | |
| AK041647 | | |
| 2010002M12RIK | | |
| CCRL2 | | |
| ISG15 | | |
| CSPRS | | |
| GM8979 | | |
| APOL9B | | |
| GM5431 | | |
| TRIM30B | | |
| SP110 | | |
| GM1966 | | |
| OAS3 | | |
| IFIH1 | | |
| OAS1G | | |
| AK172683 | | |
| HDC | | |
| TNFSF10 | | |
| CCL5 | | |
| TGTP2 | | |
| GM7609 | | |
| D130058E03 | | |
| GBP10 | | |
| OAS2 | | |
| H2-T24 | | |
| OAS1A | | |
| PYDC4 | | |
| TRIM30D | | |
| GBP6 | | |
| lIGP1 | | |
| PARP14 | | |
| SP100 | | |
| SLFN5 | | |
| TLR3 | | |
| DDX58 | | |

Gene

Expression change (Log₂)

| 7 | - | ÷ |
|---------------|---|---|
| OAS1B | | |
| MISP | | |
| GM6904 | | |
| APOL9A | | |
| SLC22A13B-PS | | |
| GVIN1 | | |
| HERC6 | | |
| DHX58 | | |
| IF147 | | |
| GPR1 | | |
| FRMD7 | | |
| GM18853 | | |
| SAMD9L | | |
| MPEG1 | | |
| TRIM30A | | |
| IL18 | | |
| GM4951 | | |
| TRIM34B | | |
| 1700123I01RIK | | |
| IRF5 | | |
| PLEKHA4 | | |
| GM4841 | | |
| EG547347 | | |
| GM12185 | | |
| BC147527 | | |
| PARP12 | | |
| CD274 | | |
| LGR5 | | |
| PTK6 | | |
| TRIM34A | | |
| KCNRG | | |
| НСК | | |
| PHF11C | | |
| SLC13A1 | | |
| BATF2 | | |
| 2010109103RIK | | |
| BCO2 | | |
| SLFN4 | | |



Expression change (Log₂)

| | 5 |
|---------------|-------|
| K035387 | |
| GM11549 | |
| .RRN2 | |
| SBP9 | |
| RIM21 | |
| .CT | |
| ITUS2 | |
| SECTM1A | |
| SLFN2 | |
| CYP26C1 | |
| JBA7 | |
| 700022I11RIK | |
| RIM72 | |
| 1607873 | |
| 930539E08RIK | |
| L6 | |
| 930111J21RIK2 | |
| RGM1 | |
| EP647 | |
| SLC15A3 | |
| DAS1H | |
| CD69 | |
| ND3C2 | |
| DNASE1L3 | |
| F135 | |
| CLEC4A1 | |
| SLFN8 | |
| CDC88B | |
| K136817 | |
| CLEC2E | |
| K014951 | |
| PARP10 | |
| CSTA1 | |
| IELZ2 | |
| PARP9 | |
| BST2 | |
| TOR3A | |
| ZD1 | |

Gene

Expression change (Log₂)

| 7 | - | |
|----------------|---|--|
| ZEB1 | | |
| PAX5 | | |
| DTX3L | | |
| TRIM12C | | |
| CTSS | | |
| IFIT2 | | |
| 9930111J21RIK1 | | |
| PSME2B | | |
| STAT1 | | |
| GM4070 | | |
| ZFP389 | | |
| OLFR461 | | |
| C130026I21RIK | | |
| MORC2B | | |
| ART3 | | |
| PIWIL4 | | |
| AK029757 | | |
| ADAM21 | | |
| ABI3BP | | |
| КМО | | |
| F830016B08RIK | | |
| DAXX | | |
| NANOG | | |
| DMRTA1 | | |
| CNKSR1 | | |
| PPP1R14D | | |
| VNN1 | | |
| MYO1B | | |
| TRIM12A | | |
| GM13710 | | |
| KIF5C | | |
| MKIAA1554 | | |
| TMEM229B | | |
| CYP26A1 | | |
| PARP11 | | |
| SERPINI2 | | |
| APOLD1 | | |
| GBP4 | | |



Expression change (Log₂)

| x | , |
|---------------|--------------|
| GM21119 | |
| AK040276 | |
| NMI | |
| LGALS9 | |
| UBE2L6 | |
| APOL10B | |
| SH2D6 | |
| PSMB10 | |
| PLSCR2 | |
| RNF213 | |
| 2610318N02RIK | |
| KLB | |
| EFCAB8 | |
| ZFP296 | |
| IFI203 | |
| TRIM25 | |
| 4930431F12RIK | |
| MNDA | |
| IFITM3 | |
| OLFR543 | |
| AK044300 | |
| SLFN10-PS | |
| SERPINB1B | |
| OLFR544 | |
| CSRNP1 | |
| SP140 | |
| AK172315 | |
| MNDAL | |
| IRF9 | |
| OLFR920 | |
| LMO2 | |
| STAT2 | |
| CLCN1 | |
| IDI2 | |
| BAAT | |
| AW011738 | |
| AK015324 | |
| BTC | |



Expression change (Log₂)

| LGALS3BP | |
|---------------|--|
| TRPM6 | |
| D6ERTD527E | |
| IL33 | |
| ADAMTS6 | |
| GM15319 | |
| NLRC5 | |
| AW112010 | |
| TMEM140 | |
| AI662270 | |
| ART2A-PS | |
| 4930459C07RIK | |
| AK033210 | |
| PLA2G4C | |
| SLFN3 | |
| OGFR | |
| BC023320 | |
| 0610043K17RIK | |
| TRAFD1 | |
| DNAH1 | |
| IL15 | |
| EIF2AK2 | |
| PDZD2 | |
| BC108341 | |
| SPINK2 | |
| C4B | |
| GM6548 | |
| OAS1C | |
| 2310001H17RIK | |
| AK142678 | |
| RAPGEF4 | |
| MITD1 | |
| CXCL13 | |
| IFI204 | |
| SERPINC1 | |
| TAS2R137 | |
| GM13939 | |
| 5430402O13RIK | |

Gene

Expression change (Log₂)

7

| . | - | |
|---------------|---|--|
| AK140192 | | |
| H2-T9 | | |
| DUSP16 | | |
| AK078307 | | |
| 9430069107RIK | | |
| SH2D5 | | |
| H2-T10 | | |
| CDHR4 | | |
| SBSPON | | |
| SYTL3 | | |
| GM595 | | |
| E130102H24RIK | | |
| C2 | | |
| AK151815 | | |
| SRRM4 | | |
| PGAM2 | | |
| ISG20 | | |
| AK157632 | | |
| BC049715 | | |
| CABLES1 | | |
| GLCCI1 | | |
| LY6E | | |
| OTOR | | |
| 9530082P21RIK | | |
| TREX1 | | |
| ZNFX1 | | |
| SMARCA5-PS | | |
| CXCL2 | | |
| CASP4 | | |
| TNF | | |
| AK088743 | | |
| TSPAN18 | | |
| 4933412E12RIK | | |
| TAP1 | | |
| DUSP28 | | |
| PHACTR1 | | |
| RASGEF1B | | |
| SLC25A22 | | |

Gene

Expression change (Log₂)

| 7 | - | 5 |
|---------------|---|---|
| DCP2 | | |
| PNPT1 | | |
| BC056174 | | |
| MOV10 | | |
| GM6568 | | |
| MSH4 | | |
| GM6634 | | |
| APOL6 | | |
| AK042126 | | |
| PPM1K | | |
| CREB5 | | |
| AA467197 | | |
| BC075659 | | |
| TRIM56 | | |
| SETDB2 | | |
| EPSTI1 | | |
| HAP1 | | |
| H2-T22 | | |
| AK084170 | | |
| APOL7A | | |
| PSMB8 | | |
| SLFN9 | | |
| IFI202B | | |
| ADAR | | |
| GNAT2 | | |
| COL9A3 | | |
| SLC3A1 | | |
| HHIPL2 | | |
| MAFK | | |
| CD40 | | |
| NMB | | |
| ZSCAN18 | | |
| SCML4 | | |
| WNT4 | | |
| G630055G22RIK | | |
| SERPINB1C | | |
| BC051226 | | |
| ZMYND12 | | |

Gene

Expression change (Log₂)

| | $\frac{1}{1}$ | , |
|---------------|---------------|--------------|
| GBP11 | | |
| CLEC2D | | |
| PARK2 | | |
| IRF1 | | |
| KCNMB4 | | |
| AU018091 | | |
| RASGRF1 | | |
| S1PR1 | | |
| AK081879 | | |
| AQP7 | | |
| SERPINB9 | | |
| NKAIN3 | | |
| ASCC3 | | |
| APOBEC1 | | |
| PTPN22 | | |
| INPP4B | | |
| LY6A | | |
| GM14137 | | |
| 4930542D17RIK | | |
| RNF114 | | |
| MSS51 | | |
| H2-T23 | | |
| SHISA5 | | |
| SLC10A6 | | |
| СКВ | | |
| TCIRG1 | | |
| A530032D15RIK | | |
| AMY1 | | |
| SERPINB6B | | |
| SAMHD1 | | |
| AFTPH | | |
| PPP1R15A | | |
| ARHGAP8 | | |
| IFI27L2A | | |
| KLHL32 | | |
| MILL2 | | |
| USP25 | | |
| IFITM6 | | |



Expression change (Log₂)

| 7 7 | |
|---------------|--|
| PRR33 | |
| AK049295 | |
| CD300LB | |
| NPY4R | |
| ZFP786 | |
| DNAJC28 | |
| NHSL2 | |
| EFNA4 | |
| CYP26B1 | |
| GAS1 | |
| 5031434C07RIK | |
| LPAR5 | |
| HEXIM2 | |
| ARL4D | |
| AKAP12 | |
| ZFP69 | |
| AK143195 | |
| AK143234 | |
| GM17455 | |
| ACOT11 | |
| AI464131 | |
| AK087024 | |
| CHST12 | |
| MAP1A | |
| TFEB | |
| SMAD6 | |
| MRGPRF | |
| 5430416O09RIK | |
| ZFP354C | |
| C5AR2 | |
| 6430571L13RIK | |
| 4632428N05RIK | |
| AK134203 | |
| HIST1H2AF | |
| OSGIN1 | |
| EFNA1 | |
| PDGFRA | |
| SPATA13 | |



Expression change (Log₂)

| Ť | - | ÷ |
|---------------|---------|---|
| AK086911 | | |
| SLC16A5 | | |
| DEPDC1B | | |
| CCDC64 | | |
| ANKRD9 | | |
| RAB3IL1 | | |
| FAM43A | | |
| ZFP418 | | |
| RALGDS | | |
| PALD1 | | |
| TNNI2 | | |
| GATSL2 | | |
| SLCO2B1 | | |
| AK038843 | | |
| NDP | | |
| RAB27A | | |
| ADCK3 | | |
| LFNG | | |
| RAB3A | | |
| G0S2 | | |
| EPHB4 | | |
| BC096455 | | |
| LPIN1 | | |
| ID1 | | |
| ARL11 | | |
| PPNR | | |
| 9430037G07RIK | | |
| SIT1 | | |
| ZFP40 | | |
| TNFAIP8L1 | | |
| 6720489N17RIK | | |
| AHDC1 | | |
| LRRC17 | | |
| DRAXIN | | |
| HELT | | |
| 4933431E20RIK | | |
| GM10825 | | |
| EPOR | | |



Expression change (Log₂)

| . | - | |
|---------------|---|--|
| PAQR7 | | |
| МАРЗК6 | | |
| TBXA2R | | |
| A4GALT | | |
| SIX5 | | |
| AK087617 | | |
| STARD9 | | |
| AQP5 | | |
| SLC22A4 | | |
| TRIM7 | | |
| LDB3 | | |
| ZFP667 | | |
| EPN3 | | |
| SIGIRR | | |
| PRICKLE2 | | |
| TBC1D2 | | |
| CYP2U1 | | |
| TRIB2 | | |
| SH2D3C | | |
| GIMAP6 | | |
| 6430550D23RIK | | |
| НҮКК | | |
| MRVI1 | | |
| CSTAD | | |
| 1110028F11RIK | | |
| TBX3 | | |
| TMEM179 | | |
| DEPTOR | | |
| MRGPRE | | |
| SNED1 | | |
| GM12522 | | |
| CAMKK1 | | |
| PIF1 | | |
| AK085891 | | |
| SESN1 | | |
| ZFP30 | | |
| ORAI1 | | |
| A930018M24RIK | | |



Expression change (Log₂)

| EMILIN1 |
|--|
| CARNS1 ITGA3 ITGA3 WNT5B ADCY9 APBB1 MKIAA1300 CXCR5 BC026208 FAM102A |
| ITGA3 ITGA3 WNT5B ITGA3 ADCY9 ITGA3 APBB1 ITGA3 MKIAA1300 ITGA3 CXCR5 ITGA3 BC026208 ITGA3 FAM102A ITGA3 |
| WNT5B Image: Constraint of the second seco |
| ADCY9 APBB1 MKIAA1300 CXCR5 BC026208 FAM102A |
| APBB1 |
| MKIAA1300 |
| CXCR5 BC026208 FAM102A |
| BC026208 |
| FAM102A |
| |
| SKIDA1 |
| MEGF9 |
| CASQ2 |
| EFNA2 |
| CCSAP |
| C130083M11RIK |
| CEACAM1 |
| SRL 📃 |
| 2900052L18RIK |
| FV1 |
| STARD8 |
| GCNT4 |
| PAPOLB |
| CASZ1 |
| DNAJC22 |
| RHEBL1 |
| HOXC5 |
| FAM117A |
| NEURL1B |
| TTLL1 |
| BC051552 |
| RNF125 |
| АКАР17В |
| |
| A530016L24RIK |
| ZFP873 |
| ARHGEF39 |
| KLHL24 |



Expression change (Log₂)

| | - | |
|---------------|---|---|
| PDCD4 | | |
| ZFP760 | = | |
| FBXO47 | | |
| C2CD2L | | |
| AK040960 | | |
| PROKR1 | | |
| RWDD2B | | |
| HIPK4 | | |
| PTGER4 | | |
| SPIN2C | | |
| LLGL2 | | |
| ATP10D | | |
| C130071C03RIK | | |
| TTC30B | | |
| ITGAL | | |
| SGMS1 | | |
| JADE2 | | |
| FAM20C | | |
| SUV420H2 | | |
| BC039771 | | |
| ZFP324 | | |
| TOB1 | | |
| AK050809 | | |
| AK039657 | | |
| MTMR4 | | |
| CDON | | |
| SAPCD2 | | |
| PGM2L1 | | |
| CCDC120 | | |
| SAT2 | | |
| AB001425 | | |
| ZBTB8A | | |
| WDR6 | | |
| 4930509E16RIK | | |
| TONSL | | |
| EPHB3 | | |
| CD9 | | Į |

Figure D. Overexpressed genes interaction network during reovirus infection.

Interaction network for the 380 cellular genes for which the expression was upregulated upon viral infection. The network was determined by uploading the genes into STRING. Solid lines: direct known interactions; dashed lines: suspected or indirect interactions.

Figure D



Vish4

Figure E. 240 ASEs are modified during viral infection with reovirus.

Heatmap representation with a sequential color scale of the 240 ASEs that are differentially spliced upon viral infection. RNA sequencing was done in triplicate for both the uninfected (mock) and infected cells. Darker shades indicates high Δ PSI values and lighter shades indicates low Δ PSI values between infected and mock cells. More than one ASEs can impact the same gene.

| ABI1 CLDN12 GPBP1 NABP1 RBPJ TCF12 CLIP1 GTF2A2 NAIP2 RBPMS TCF25 ILX2 ACM1 CLN4 GVIN1 NASP RIF1 TMEM188 ILX2 ACM1 CLN4 GVIN1 NASP RIF1 TMEM188 IXX2 ACMAT CNOT4 HINR12 NCOAT RNF135 TMEM19 IXMEM19 ADAR COBL1 HINRNPA2B1 NCOAT RNF135 TMEM19 IXMEM19 AGKR01 CPSF6 HINRPA2B1 NCOR1 RNF135 TMEM19 IXMEM19 ANKR010 CPSF6 HINRPC NEMF TR2A2A IXMEM1 RSRC2 TP22 IXMEM1 APOL9A NAM1 MARP21 NEMF TR2A2A IXMP21 IXMA TRP2A2A IXMEM1 IXMEM2A RSRC2 TTP22 IXMEM1 IXMEM2A IXMEM1 IXMEM2A IXMEM2A IXMEM2A IXMEM2A IXMEM2A IXMEM2A IXMEM2A IXMEM2A IXMEM2A </th <th>Gene</th> <th>Gene</th> <th>Gene</th> <th>ΔΡSI</th> <th>Gene</th> <th>Gene</th> <th>Gene</th> <th>ΔPSI</th> | Gene | Gene | Gene | ΔΡSI | Gene | Gene | Gene | ΔPSI |
|--|-----------|---------|------------|------|----------|---------|----------------|------|
| ACIN1 CLIP1 GTF2A2 NAIP2 REMNS TCF25 ACIN1 CLK4 GVIN1 NAIP2 RFX5 TLK2 A ADAR CNOT4 HBS1L NCOA7 RNF13 TMEM132A A AGRG GOBL1 HIRGA1 NCOR1 RNF13 TMEM168 A AGRG1 HIRMPA281 NDE1 RNF13 TMEM168 A ANKRD10 CPSF6 HNRNPC NED4L RSRC1 TNIP1 A ANKRD11 CWC22 HPS3 NEMF RSRC2 TPP2 A ARHGAP12 DST HUWE1 NEMF TRAPC13 TRAPC13 TRAPC13 ASAP1 IL34 NPA2 SAMHD1 TXXLAA TSPAN9 A ASAP1 IL34 NPA2 SAMHD1 TXXLAA MBAP1 MBAP1 ATXT1 ECC2 IQCE OPA1 SCAF11 UBAP1 MBAP1 BTRC TXTALA MATA PAFA9 SENP6 | ABI1 | CLDN12 | GPBP1 | | NABP1 | RBPJ | TCF12 | |
| ACIMI CLIP1 WAP2 RFX5 TLK2 ACM1 CLK4 GVINI NASP RiF1 TMEM132A ADAR CO014 HBS1L NCOAT RNF13 TMEM132A ADAR COBL1 HMGA1 NCOAT RNF13 TMEM192A ADR COBL1 HMGA1 NCORT RNF13 TMEM192A ANKRD10 CPSF6 HNRNP2E NEDD4L RNSRC1 TMIP1 ANKRD11 CWC22 HPS3 RSRC2 TP2 TRA2A APOL9A HUWE1 NEMF RSRC1 TRA2A TRA2A ARHGAP12 DCAF10 IF1203 NEMF TRA2A TRA2A ASAP1 L134 NIPA2 SAMHD1 TRAPC13 TRA2A ASAP1 E2F3 ILF3 ODF2L UBA2+1 UBA2+1 ATXM11 ECE2 IGCE OPA1 SCAF11 UBR2 BRA EIF42 JMID1C PARP9 SENP6 UBR3 < | | | GTF2A2 | | | RBPMS | TCF25 | |
| ACINI CLK4 GVINI NASP RIF1 TMEM132A ADAM17 CN014 HBS1L NCOAT RNF13 TMEM168 A ADAR COBL1 HBS1L NCOAT RNF13 TMEM168 A AGFG1 HINRNPA2B1 NCCR1 RNPS1 TMEM168 A ARKRD10 CPSF6 HINRNPA2B1 NDE1 RNPS1 TMPO A ANKRD11 CWC22 HPS3 NEK1 RSRC1 TMPO A ARHGAP12 DCAF10 IF1203 NEMF RSRX1 TRA2A A ARHGAP12 DST IF1203 NEXN TRPC4AP TRA2A A ASAP1 IF3 ODF2L TSPAN9 TSPAN9 TSPAN9 A ASAP1 IF3 ODF2L VIN14 UBAP1 UBAP1 UBAP1 UBAP1 A ASAP1 IF3 ODF2L VIN44 UBAP1 UBAP1 UBAP1 A ASPH E2F3 < | | CLIP1 | | | NAIP2 | RFX5 | TLK2 | |
| ADAM77 CNO74 HBS1L NCOR1 RNF13 TMEM168 ADAR COBLL1 HMGA1 NCOR1 RNF135 TMEM19 ADAR COBL1 HMRA1 NCOR1 RNF135 TMEM19 ADAR COBL1 HMRNP2B1 NCOR1 RNF135 TMEM19 ANKRD10 CPSF6 HMRNP2B1 NDE1 RNF13 TMEM168 ANKRD11 CWC22 HPS3 TMEW1 RSRC1 TMPO ARIGAP11A DCAF10 HIVWE1 NEMF TRP24A TRP24A ARIGAP11A DCAF10 IL34 NEXN TSPAN9 TSPAN9 ASAP1 E2F3 ILF3 ODF2L UBAP1 UBAP1 ATXT/1 ECC2 IQCE OPA1 SCAF11 UBR2 BNP2 INSCA PAR9 SENP6 UBR3 IMB1 BNP4 ECT3 IVNS1ABP PHACTR4 SKIL VLDLR VDLR BNR4 EIF4A2 JMUD1C PIGAT4 S | ACIN1 | CLK4 | GVIN1 | | NASP | RIF1 | TMEM132A | |
| ADAR COBLL1 HMGA1 NCR1 RNF135 THEM19 AGFG1 AGRG1 HNRNPA2B1 NDE1 RNPS1 TMPO ANKRD10 CPSF6 HNRNPC NEDJL RNSC1 TNP1 ANKRD11 CWC22 HPS3 NEK11 RSC2 TNP1 ARHGAP12 DCAF10 IFI203 NEMF TRA2A ITRPC4AP ARHGAP12 DST NEXX TRPC4AP TSPAN9 ITRPC4AP ASAP1 IL34 NIPA2 SAMHD1 TXNL4A IUBR2 ASAP1 IL73 OP21 UBR2 SAMHD1 UBR2 IUBR2 BNIP2 IGSEC2 ICSEC2 OP21 UBR2 IUBR2 IUBR2 IUBR2 BNIP2 PAN3 SENP1 IUBR2 SAMHD1 TXNL4A IUBR2 I | ADAM17 | CNOT4 | HBS1L | | NCOA7 | RNF13 | TMEM168 | |
| AGFG1 | ADAR | COBLL1 | HMGA1 | | NCOR1 | RNF135 | TMEM19 | |
| ANKRD10 CPSF6 HNRNPC NEDD4L RSRC1 TWP1 A ANKRD11 CWC22 HPS3 NEMF RSRC2 TWP1 TRA2A APOL9A DCAF10 IF203 NEMF TRA2A TRA2A TRA2A ARHGAP12 DST IF203 NEMF TRAPC13 TRAPC13 TRAPC14P ASAP1 IL34 NFX1 TRAPC4AP TSPAN9 TSPAN9 III ASPH E2F3 ILF3 ODF2L SAMHD1 UBAP1 UBAP1 ATX71.1 ECE2 IQCE OPA1 SCAF11 UBR2 UBR3 BNIP2 FGF5 SFI1 UBR3 III IIII IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | AGFG1 | | HNRNPA2B1 | | NDE1 | RNPS1 | ТМРО | |
| ANKRD11 CWC22 HPS3 NEK1 RSRC1 TNIP1 APOLSA HUWE1 NEMF RSRC2 TP22 ARHGAP11A DCAF10 IF1203 NEMF TRA2A ARHGAP12 DST II.34 NENK TRPC4AP ASAP1 II.34 NIPA2 SAMHD1 TSPAN9 ASAP1 II.34 ODF2L UBAP1 UBAP1 ATAT1 ECE2 IQCE OP11 SCAF11 UBAP1 BNIP2 II.SEC2 PAN3 SENP6 UBR3 IIII BNIP2 II.SEC2 PAR9 SENP6 UBR3 IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | ANKRD10 | CPSF6 | HNRNPC | | NEDD4L | | | |
| ANKRD11 CWC22 HPS3 NEWF RSRC2 TPP2 Image: Constraint of the second sec | | | | | NEK1 | RSRC1 | TNIP1 | |
| APOL9A ARHGAP11A DCAF10 HUWE1 NEMF RTM4 TRA2A ARHGAP11A DCAF10 HI/203 NEURL4 RTM4 TRA2A III ARHGAP12 DST III.34 NEXN NEXN TSPAN9 IIII ASAP1 III.73 ODF2L SAMHD1 TSPAN9 IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | ANKRD11 | CWC22 | HPS3 | | | RSRC2 | TPP2 | |
| ARHGAP11A DCAF10 IFI203 NEURL4 RTN4 TRAPPC13 III ARHGAP12 DST III NEXN NEXN TRPC4AP III ASAP1 IIII IIII NIFA1 TRPC4AP TRPC4AP IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | APOL9A | | HUWE1 | | NEMF | | TRA2A | |
| ARHGAP12 DST II.34 NEXN NFX1 TRPC4AP TSPAN9 ASAP1 II.34 NIPA2 SAMHD1 TXNL4A III.44 ASPH E2F3 II.F3 ODF2L TXNL4A III.44 ATXAT1 ECE2 IQCE OPA1 SCAF11 UBR2 III.87 ATXNT.1 ECT2 IQSEC2 PAR9 SENP6 UBR3 III.83 BNP2 IQSEC2 PAR9 SENP6 UBR3 III.83 < | ARHGAP11A | DCAF10 | IFI203 | | NEURL4 | RTN4 | TRAPPC13 | |
| ARH6AP12 DST IL34 NFX1 TSPAN9 ASAP1 IL34 NIPA2 SAMHD1 TXNL4A ASPH E2F3 ILF3 ODF2L UBAP1 ATAT1 ECC2 IQCE OPA1 SCAF11 UBR2 ATXN11 ECT2 IQSEC2 PAR9 SENP1 UBR3 BNP2 IQSEC2 PARP9 SENP6 UBR3 Image: Comparison of the compar | | DNM1L | | | NEXN | | TRPC4AP | |
| ASAP1 II.34 NIPA2 SAMHD1 TXNL4A ASPH E2F3 ILF3 ODF2L UBAP1 UBAP1 ATAT1 ECE2 IQCE OPA1 SCAF11 UBR2 IDSP2 BNIP2 IQSEC2 PAN3 SENP1 UBR3 IDSP3 BNIP2 IQSEC2 PARP9 SENP6 UBR3 IDSP3 BRD4 EIF4A2 JMJD1C PIGA SFSWAP UPF1 IDSP1 BRD4 EIF4A2 JMJD1C PIGA SSL23A2 WSB1 IDSP1 CAUU KAT6A PITPNB SLC3A2 WSB1 IDSP1 IDSP1 IDSP1 CAMK2D EIF4H KMT2E POLG2 SMC5 ZFML IDSP1 IDSP1 <td< td=""><td>ARHGAP12</td><td>DST</td><td></td><td></td><td>NFX1</td><td></td><td>TSPAN9</td><td></td></td<> | ARHGAP12 | DST | | | NFX1 | | TSPAN9 | |
| ASPH E2F3 ILF3 ODF2L UBAP1 UBAP1 ATAT1 ECE2 IQCE OPA1 SCAF11 UBR2 ATXN7L1 ECT2 IQSEC2 PARP9 SENP1 IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | ASAP1 | | IL34 | | NIPA2 | SAMHD1 | TXNL4A | |
| ATAT1 ECE2 IQCE OPA1 SCAF11 UBR2 ATAT1 ATXNT11 ECT2 IQSEC2 PAN3 SENP1 IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | ASPH | E2F3 | ILF3 | | ODF2L | | UBAP1 | |
| ATXN7L1 ECT2 IQSEC2 PAN3 SENP1 IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | ATAT1 | ECE2 | IQCE | | OPA1 | SCAF11 | UBR2 | |
| BNIP2 Image: Second | ATXN7L1 | ECT2 | | | PAN3 | SENP1 | | |
| BORA BPTF EDC3 IVNS1ABP PCGF5 SFI1 III III IIII IIII IIIII IIIIIII IIIIIIIIIII IIIIIIIIIIIIIIIIIIIIII IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | BNIP2 | | IQSEC2 | | PARP9 | SENP6 | UBR3 | |
| BPTF EDC3 IVNS1ABP PHACTR4 SFSWAP UPF1 Important of the second | BORA | | | | PCGF5 | SFI1 | | |
| BRD4 EIF4A2 JMJD1C PIGA SKIL VLDLR PIGA BTRC KAT5 PITPNB SLC23A2 WSB1 PIGA SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PIGA PITPNB SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PITPNB SLC23A2 WSB1 PIGA PIGA PITPNB SLC23A2 WSB1 PIGA PIGA PITPNB SLC23A2 WSB1 PIGA PIGA SLC23A2 WSB1 PIGA SLC23A2 WSB1 PIGA SLC23A2 WSB1 PIGA SLC23A2 SLFN3 SLFN3 ZHI PIGA PIGA PIGA SLFN3 SLFN3 SLFN3 ZFML PIGA PIGA PIGA PIGA SUFN3 PIGA PIFPICA SUFN3 SUFN3 ZFP207 PIGA PIGA PIGA PIGA PIGA PIGA PIGA SUFN3 PIGA PIFPICA | BPTF | EDC3 | IVNS1ABP | | PHACTR4 | SFSWAP | UPF1 | |
| BTRCKAT5PITPNBSLC23A2WSB1CALUKAT6APNPLATSLFN3XDHCAMK2DEIF4HKMT2EPOLG2SKC5ZFMLERBB2IPLRRFIP1PPFIBP1ZFP207ZFP207MACF1PPP1R12ASONZFP207CCBWD1MAXPQLC1SPEF2ZFP788CCDC136FAM179BPREPLSPOPLZMYND11CCDC15FAM78BMBNL2PRFF39SRGAP2ZMYND8CCNCFBX034MDM2PUM2SRSF3ZYXCCNL1FLCNMFFQKSRSF51700057G04RIKCDKN2AIPF0XK2MFSD4 | BRD4 | EIF4A2 | JMJD1C | | PIGA | SKIL | VLDLR | |
| CALUKAT6APNPLA7SLFN3XDHCAMK2DEIF4HKMT2EPOLG2SMC5ZFMLZFMLCAMKK2Image: Campute constraints of the constraint of the constraints of the constraint of th | BTRC | | KAT5 | | PITPNB | SLC23A2 | WSB1 | |
| CAMK2DEIF4HKMT2EPOLG2SMC5ZFMLZFMLCAMKK2ERI3LRRFIP1PPFIBP1PPFIBP1IIZFP207ICBWD1ERI3MATR3PPP1R12ASONIIIIICCDC136FAM179BMAXPREPLSPOPLZFP788IICCDC15FAM78BMBNL2PRF39SRGAP2ZMYND11IICCNCFBX034MDM2PUM2SRSF3ZYXII700057G04RIKICCNL1FLCNMFFQKSRSF51700057G04RIKIIIICDKN2AIPF0XK2MFSD4IIIIIIIII | CALU | | KAT6A | | PNPLA7 | SLFN3 | ХDH | |
| CAMKK2ERBB2IPLRRFIP1PPFIBP1ZFP207CAMKK2ERI3MACF1PPFIBP1SONZFP207CBWD1MAXPQLC1SPEF2ZFP788CCDC136FAM179BMAXPREPLSPOPLZMYND11CCDC15FAM78BMBNL2PRPF39SRGAP2ZMYND8CCNCFBX034MDM2PUM2SRSF3ZYXCCNL1FLCNMFFQKSRSF51700057G04RIKCDKN2AIPFOXK2MFSD4 | CAMK2D | EIF4H | KMT2E | | POLG2 | SMC5 | ZFML | |
| CAMKK2MACF1MACF1PPP1R12ASONInterviewCBWD1MATR3MATR3PQLC1SPEF2ZFP788InterviewCCDC136FAM179BMAXPREPLSPOPLZMYND11InterviewCCDC15FAM78BMBNL2PRPF39SRGAP2ZMYND8InterviewCCNCFBX034MDM2QKSRSF3ZYXInterviewCCNL1FLCNMFFQKSRSF51700057G04RIKInterview | | ERBB2IP | LRRFIP1 | | PPFIBP1 | | ZFP207 | |
| ERI3MATR3PQLC1SPEF2ZFP788CBWD1MAXPQLC1SPOPLZMYND11CCDC136FAM179BPREPLSPOPLZMYND11CCDC15FAM78BMBNL2PRPF39SRGAP2ZMYND8CCNCFBX034MDM2PUM2SRSF3ZYXCCNL1FLCNMFFQKSRSF51700057G04RIKCDKN2AIPFOXK2MFSD4 | CAMKK2 | | MACF1 | | PPP1R12A | SON | | |
| CBWD1MAXMAXPREPLSPOPLZMYND11CCDC136FAM179BPREPLPREPLSPOPLZMYND11CCDC15FAM78BMBNL2PRF539SRGAP2ZMYND8CCNCFBX034MDM2PUM2SRSF3ZYXCCNL1FLCNMFFQKSRSF51700057G04RIKCDKN2AIPFOXK2MFSD42210018M11RIK | | ERI3 | MATR3 | | PQLC1 | SPEF2 | ZFP788 | |
| CCDC136FAM179BMBNL2PRPF39SRGAP2ZMYND8CCDC15FAM78BMBNL2PUM2SRSF3ZYXICCNCFBX034MDM2QKSRSF3ZYXICCNL1FLCNMFFQKSRSF51700057G04RIKICDKN2AIPFOXK2MFSD4IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII | CBWD1 | | MAX | | PREPL | SPOPL | ZMYND11 | |
| CCDC15 FAM78B MBNL2 PUM2 SRSF3 ZYX Image: Constraint of the constra | CCDC136 | FAM179B | | | PRPF39 | SRGAP2 | ZMYND8 | |
| CCNC FBX034 MDM2 FORME FORME <thf< td=""><td>CCDC15</td><td>FAM78B</td><td>MBNL2</td><td></td><td>PUM2</td><td>SRSE3</td><td>ZYX</td><td></td></thf<> | CCDC15 | FAM78B | MBNL2 | | PUM2 | SRSE3 | ZYX | |
| CCNL1 FLCN MFF GIN | CCNC | FBXO34 | MDM2 | | OK | SRSF5 | 1700057G04RIK | |
| CDKN2AIP FOXK2 MFSD4 | CCNL1 | FLCN | MFF | | Q, t | | 2210018M11RIK | |
| RAB100S STAM | CDKN2AIP | FOXK2 | MFSD4 | | RAB100S | STAM | | |
| CELF1 G2E3 MICAL3 RAB64 STX3 2310057M21RIK | CELF1 | G2E3 | MICAL3 | | RAB64 | STX3 | 2310057M21RIK | |
| GAPVD1 MIS18BP1 RADOR SIJV39H2 2410002E23BIK | | GAPVD1 | MIS18BP1 | | RANBP3 | SUV39H2 | 2410002F23RIK | _ |
| GAS5 MON2 RBM39 TACC2 2810474010PIK | | GAS5 | MON2 | | RBM39 | TACC2 | 2810474019RIK | |
| CELF2 GDAP2 MORN1 Relins Action Control Contro | CELF2 | GDAP2 | MORN1 | | (Lenico | | 4631405 119RIK | |
| CFLAR GEN1 MSH4 403/14030/19/K/K | CFLAR | GEN1 | MSH4 | | RBM4 | | 49305031 19RIK | |
| | | GLS | WH 11-3 | | | TRP | 4930511M06RIK | |

Figure E

Figure F. Profiling of the cellular alternative splicing landscape during reovirus infection.

(A) Interaction network for genes encoding the 240 differentially spliced transcripts upon viral infection. The network was determined by uploading the corresponding genes into STRING. Solid lines: direct known interactions; dashed lines: suspected or indirect interactions.

(B) Gene ontology analysis of the 240 differentially spliced transcripts upon viral infection. The corresponding genes were imported into the DAVID gene ontology suite of programs at the NIAID. Ontological functions were determined determined for biological processes using all ASEs caracterized as background.



-(Log₁₀) Pvalue (Bonferroni Correction)

Figure G. Additional validation of ASEs dysregulated in infected cells.

(A, C, E) Overview of two isoforms encoded by the *HNRNPA2B1*, *EIF4A2*, and *IL34* genes. Exons are depicted in red and and the intervening introns are shown as thin black lines (not to scale). The primers used to detect the ASEs by RT-PCR assays are shown in gray and the sizes of the expected amplicons (162 nt and 282 nt, 112 nt and 219 nt, 256 nt and 374 nt, respectively) are also indicated. The genomic coordinates of the two isoforms are also indicated.

(B, D, F) Cellular mRNAs isolated from both uninfected and infected cells were analyzed by RT-PCR using specific primers to detect both forms of the ASE encoded on various genes. The amplified products were analyzed by automated chip-based microcapillary electrophoresis. Capillary electrophoregrams of the PCR reactions are shown. The positions and the amplitude of the detected amplicons are highlighted by red boxes. The positions of the internal markers are also indicated.



HNRNPA2B1 - Infected

HNRNPA2B1 - Uninfected





EIF4A2 - Uninfected

EIF4A2 - Infected





IL34 – Uninfected

IL34 - Infected



Figure H. List of the differentially ASEs associated with viral infection.

The list displays the 240 differentially spliced transcripts with the corresponding Delta PSI values, the associated gene expression (in Log₂), and the associated biological processes.



Figure H











Figure I. Common ASEs modified between WT reovirus and P4L-12 mutant show a strong correlation.

Correlation between PSI values for WT and P4L-12 mutant reovirus.



Figure J. Analysis of the 240 differnentially spliced transcripts highlights a consensus sequence.

A significant enrichment of a 41 nt motif in the vicinity of many splice regions was found in transcripts for which AS was altered upon viral infection. The motif was found in 93 of the 240 transcripts that were differentially spliced upon viral infection (e value = $1,3e-10^{49}$). The differentially spliced exon and its flanking introns were used to search for this motif.

