Supporting Information

Characterization of FUS mutations in amyotrophic lateral sclerosis using RNA-Seq

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Figure S3. FUS protein levels measured by western blot.

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Materials and Methods S1. Formulas used for RNA-Seq analysis.

Exon Skipping: $\log _{2}$ (Inclusion: Skip + General Ratio) in the two groups, respectively. In formula LISGR1 $=\log _{2}((j u p 1+e a l 1+j d n 1) /(e u p 1+j s k 1+e d n 1))$ and analogously for LISGR2.

Intron Retention: $\log _{2}$ (Intron: Flank Ratio). Log-Odds-Ratio (Flanking). In formula LORF = LIFR2 LIFR1. The sign convention means that higher value indicates more intron retention (unspliced isoform) in the second group. This indicates the level of the intron relative to the flanking exons.

More detailed information regarding terms and definitions can be found on the ExpressionPlot website (http://www.expressionplot.com/wiki/index.php?title=Project_directory_structure) and corresponding manuscript [17].

## Table S1. Summary of RNA-Seq analysis.

| Sample | No. Reads | No. Reads <br> Passing QC | \% Passing <br> QC | Uniquely <br> Mapping | \% Uniquely <br> mapping | No. <br> Ribosomal | \% <br> Ribosomal | Splice <br> Junctions | \% Splice <br> Junctions |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| Wild-type | $31,051,162$ | $31,022,757$ | 99.91 | $21,865,318$ | 70.48 | 446,094 | 2.04 | $2,222,084$ | 10.16 |
| R521G | $31,077,360$ | $31,057,750$ | 99.94 | $21,710,924$ | 69.91 | 488,727 | 2.25 | $2,292,605$ | 10.56 |
| R522G | $24,491,122$ | $24,476,034$ | 99.94 | $17,427,598$ | 71.20 | 474,659 | 2.72 | $1,754,345$ | 10.07 |
| siRNA | $28,196,024$ | $28,179,703$ | 99.94 | $20,640,291$ | 73.25 | 291,210 | 1.41 | $2,242,343$ | 10.86 |
| Vector | $27,295,832$ | $27,273,639$ | 99.92 | $19,416,054$ | 71.19 | 421,688 | 2.17 | $1,983,350$ | 10.22 |
| Average | $28,422,300$ | $28,401,977$ | 99.93 | $20,212,037$ | 71.20 | 424,476 | 2.12 | $2,098,945$ | 10.37 |

Table S2. Functional annotation KEGG pathways.

| Analysis | Group | KEGG pathway | Count | $P$-value | Benjamini |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Differential expression | FUS-WT vs. vector | Ribosome | 14 | 5.6E-6 |  |
|  |  |  |  |  | 7.2E-4 |
|  | siRNA vs. vector | Spliceosome | 34 | 7.1E-11 | 1.2E-8 |
|  |  | Ribosome | 26 | 1.9E-9 | 1.6E-7 |
|  | R521G vs. vector | Spliceosome | 18 | 4.4E-10 | 4.1E-8 |
|  | R522G vs. vector | Ribosome | 15 | 3.1E-8 | 3.1E-6 |
|  |  | Spliceosome | 15 | 3.3E-6 | 1.7E-4 |
|  |  | Mismatch repair | 6 | 2.4E-4 | 8.2E-3 |
|  |  | DNA replication | 7 | 2.7E-4 | 6.8E-3 |
|  |  | Cell cycle | 11 | 1.3E-3 | 2.6E-2 |
| Skipped exons | FUS-WT vs. vector | N/A | N/A | N/A | N/A |
|  | siRNA vs. vector | Ribosome | 18 | 8.6E-11 | 8.9E-9 |
|  |  | Spliceosome | 17 | 2.0E-7 | 1.1E-5 |
|  | R521G vs. vector | Ribosome | 6 | 1.6E-4 | 6.7E-3 |
|  | R522G vs. vector | Spliceosome | 6 | 3.7E-4 | 1.4E-2 |
|  |  | Ribosome | 5 | 9.0E-4 | 1.6E-2 |
| Retained introns | FUS-WT vs. vector | Spliceosome | 50 | 1.0E-16 | 1.9E-14 |
|  |  | Huntington's disease | 54 | 3.9E-12 | 3.3E-10 |
|  |  | Proteasome | 21 | 2.7E-8 | 1.5E-6 |
|  |  | Parkinson's disease | 37 | 4.9E-8 | 2.1E-6 |
|  |  | Oxidative phosphorylation | 37 | 7.6E-8 | 2.6E-6 |
|  |  | Cell cycle | 36 | 8.6E-8 | 2.4E-6 |
|  |  | DNA replication | 17 | 3.3E-7 | 7.9E-6 |
|  |  | Pyrimidine metabolism | 29 | 5.5E-7 | 1.2E-5 |
|  |  | RNA polymerase | 14 | 2.3E-6 | 4.4E-5 |
|  |  | Aminoacyl-tRNA biosynthesis | 17 | 2.7E-6 | 4.6E-5 |
|  |  | Alzheimer's disease | 38 | 9.9E-6 | 1.5E-4 |
|  |  | Nucleotide excision repair | 16 | 3.8E-5 | 5.3E-4 |
|  |  | Citrate cycle (TCA cycle) | 13 | 5.4E-5 | 7.0E-4 |
|  |  | Purine metabolism | 33 | 2.1E-4 | 2.5E-3 |
|  |  | Mismatch repair | 10 | 4.3E-4 | 4.9E-3 |
|  |  | RNA degradation | 15 | 2.8E-3 | 2.9E-2 |
|  | siRNA vs. vector | Spliceosome | 57 | 1.4E-22 | 2.4E-20 |
|  |  | Huntington's disease | 54 | $2.4 \mathrm{E}-12$ | 2.0E-10 |



|  | Aminoacyl-tRNA biosynthesis | 15 | $1.3 \mathrm{E}-5$ | $2.4 \mathrm{E}-4$ |
| :--- | :--- | :--- | :--- | :--- | :--- |
|  | Parkinson's disease | 29 | $1.8 \mathrm{E}-5$ | $2.9 \mathrm{E}-4$ |
|  | Oxidative phosphorylation | 27 | $1.7 \mathrm{E}-4$ | $2.6 \mathrm{E}-3$ |
|  | Alzheimer's disease | 30 | $6.1 \mathrm{E}-4$ | $8.3 \mathrm{E}-3$ |
|  | Citrate cycle (TCA cycle) | 10 | $1.8 \mathrm{E}-3$ | $2.2 \mathrm{E}-2$ |
|  | Nucleotide excision repair | 12 | $2.2 \mathrm{E}-3$ | $2.5 \mathrm{E}-2$ |
|  | RNA degradation | 14 | $2.2 \mathrm{E}-3$ | $2.4 \mathrm{E}-2$ |

Abbreviations: FUS-WT = cell lines transfected with human FUS wild-type, used as a model for overexpression, siRNA = cell lines transfected with FUS small interfering RNA (siRNA), used as a model for underexpression, R521G = p.Arg521Gly, R522G $=$ p.Arg522Gly, and N/A $=$ not applicable. Significant KEGG pathways are shown for each condition. Homo sapiens is used as background, in Table 1 the Vector alone is used as background. Genes are specified in Table S3.

Table S3. Differentially expressed genes present within identified KEGG pathways.

| Group | $\begin{aligned} & \hline \text { KEGG } \\ & \text { pathway } \\ & \hline \end{aligned}$ | Name | Description |
| :---: | :---: | :---: | :---: |
| FUS-WT vs. vector | Ribosome | RPL13 | ribosomal protein L13 |
|  |  | RPL18 | ribosomal protein L18 |
|  |  | RPL26 | ribosomal protein L26 |
|  |  | RPL29 | ribosomal protein L29 |
|  |  | RPL37A | ribosomal protein L37a |
|  |  | RPL8 | ribosomal protein L8 |
|  |  | RPS11 | ribosomal protein S11 |
|  |  | RPS16 | ribosomal protein S16 |
|  |  | RPS19 | ribosomal protein S19 |
|  |  | RPS3 | ribosomal protein S3 |
|  |  | RPS4X | ribosomal protein S4X |
|  |  | RPS6 | ribosomal protein S6 |
|  |  | RPLP0 | ribosomal protein, large, P0 |
|  |  | RPLP2 | ribosomal protein, large, P2 |
| siRNA vs. vector | Spliceosome | DDX23 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 23 |
|  |  | DDX46 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 46 |
|  |  | BAT1 | HLA-B associated transcript 1 |
|  |  | LSM2 | LSM2 homolog, U6 small nuclear RNA associated |
|  |  | PRP19 | PRP19/PSO4 pre-mRNA processing factor 19 homolog |
|  |  | PRPF40A | PRP40 pre-mRNA processing factor 40 homolog A |
|  |  | PRPF8 | PRP8 pre-mRNA processing factor 8 homolog |
|  |  | RBM17 | RNA-binding motif protein 17 |
|  |  | RBM25 | RNA-binding motif protein 25 |
|  |  | THOC2 | THO complex 2 |
|  |  | THOC4 | THO complex 4 |
|  |  | U2AFBP | U2 small nuclear RNA auxiliary factor 1 |
|  |  | SR140 | U2-associated SR140 protein |
|  |  | ACIN1 | apoptotic chromatin condensation inducer 1 |
|  |  | EFTUD2 | elongation factor Tu GTP binding domain containing 2 |
|  |  | HSPA1A | heat shock 70kDa protein 1B |
|  |  | HSPA8 | heat shock 70kDa protein 8 |





|  | MCM7 | minichromosome maintenance complex component 7 |
| :--- | :--- | :--- |
|  | PLK1 | polo-like kinase 1 (Drosophila) |
| PCNA | proliferating cell nuclear antigen |  |
| YWHAE | similar to 14-3-3 protein epsilon (14-3-3E) |  |
| PRKDC | similar to protein kinase, DNA-activated, catalytic polypeptide |  |
| STAG2 | stromal antigen 2 |  |
| YWHAQ | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, <br> theta polypeptide |  |

Table S4. Significant protein domains present in differentially expressed genes.

| Group | INTERPRO | Count | P-value | Benjamini |
| :---: | :---: | :---: | :---: | :---: |
| FUS-WT vs. vector | RNA recognition motif, RNP-1 | 20 | 7.2E-7 | 6.0E-4 |
|  | Endoplasmic reticulum, targeting sequence | 10 | 9.2E-7 | 3.8E-4 |
|  | Nucleotide-binding, alpha-beta plait | 17 | 5.2E-5 | 1.4E-2 |
| siRNA vs. vector | Nucleotide-binding, alpha-beta plait | 48 | 3.2E-14 | 5.4E-11 |
|  | RNA recognition motif, RNP-1 | 46 | 4.1E-13 | 3.5E-10 |
|  | Zinc finger, PHD-type | 19 | 1.2E-5 | 6.6E-3 |
|  | Zinc finger, PHD-finger | 18 | 2.1E-5 | 8.6E-3 |
|  | Helicase, superfamily 1 and 2, ATP-binding | 20 | 4.0E-5 | 1.3E-2 |
|  | DEAD-like helicase, N -terminal | 20 | 5.2E-5 | 1.5E-2 |
|  | Actinin-type, actin-binding, conserved site | 9 | 5.4E-5 | 1.3E-2 |
|  | Zinc finger, PHD-type, conserved site | 18 | 6.9E-5 | 1.4E-2 |
|  | K Homology | 11 | 7.4E-5 | 1.4E-2 |
|  | DNA/RNA helicase, C-terminal | 19 | 1.3E-4 | 2.2E-2 |
| R521G vs. vector | RNA recognition motif, RNP-1 | 28 | 1.9E-15 | 1.2E-12 |
|  | Nucleotide-binding, alpha-beta plait | 27 | 2.0E-14 | 6.3E-12 |
|  | DNA/RNA helicase, C-terminal | 12 | $4.3 \mathrm{E}-6$ | 8.9E-4 |
|  | Helicase, superfamily 1 and 2, ATP-binding | 12 | 4.3E-6 | 8.9E-4 |
|  | DEAD-like helicase, N -terminal | 12 | 5.2E-6 | 8.0E-4 |
|  | Zinc finger, PHD-finger | 10 | 2.6E-5 | 3.2E-3 |
|  | Zinc finger, PHD-type | 10 | 4.1E-5 | 4.2E-3 |
|  | DNA-binding SAP | 6 | 5.2E-5 | 4.6E-3 |
|  | SNF2-related | 6 | $2.7 \mathrm{E}-4$ | 2.1E-2 |
|  | K Homology, type 1 | 6 | $3.1 \mathrm{E}-4$ | 2.1E-2 |
|  | K Homology, type 1, subgroup | 6 | 4.2E-4 | 2.5E-2 |
|  | K Homology | 6 | $5.4 \mathrm{E}-4$ | $3.0 \mathrm{E}-2$ |
| R522G vs. vector | Nucleotide-binding, alpha-beta plait | 20 | 9.2E-9 | 6.3E-6 |
|  | RNA recognition motif, RNP-1 | 19 | 4.6E-8 | 1.6E-5 |
|  | HEAT | 10 | 5.0E-7 | 1.1E-4 |
|  | Armadillo-like helical | 13 | $3.1 \mathrm{E}-6$ | 5.3E-4 |
|  | RNA helicase, ATP-dependent, DEAD-box, conserved site | 7 | 1.9E-5 | 2.6E-3 |
|  | Chaperonin TCP-1, conserved site | 5 | 1.9E-5 | 2.2E-3 |


| Helicase, superfamily 1 and 2, ATP-binding | 11 | 2.1E-5 | 2.1E-3 |
| :---: | :---: | :---: | :---: |
| DNA/RNA helicase, C-terminal | 11 | $2.1 \mathrm{E}-5$ | 2.1E-3 |
| DEAD-like helicase, N -terminal | 11 | $2.5 \mathrm{E}-5$ | $2.1 \mathrm{E}-3$ |
| Chaperone, tailless complex polypeptide 1 | 5 | $3.0 \mathrm{E}-5$ | $2.2 \mathrm{E}-3$ |
| Nucleic acid-binding, OB-fold | 8 | 4.1E-5 | $2.8 \mathrm{E}-3$ |
| RNA helicase, DEAD-box type, Q motif | 7 | $4.5 \mathrm{E}-5$ | $2.8 \mathrm{E}-3$ |
| DNA/RNA helicase, DEAD/DEAH box type, N-terminal | 8 | $1.0 \mathrm{E}-4$ | $5.8 \mathrm{E}-3$ |
| Importin-beta, N-terminal | 5 | 1.2E-4 | 6.1E-3 |
| Chaperonin Cpn60/TCP-1 | 5 | 1.2E-4 | $6.1 \mathrm{E}-3$ |
| DNA-dependent ATPase MCM, conserved site | 4 | $2.9 \mathrm{E}-4$ | $1.4 \mathrm{E}-2$ |
| DNA-dependent ATPase MCM | 4 | 4.4E-4 | $2.0 \mathrm{E}-2$ |
| ATPase, F1/V1/A1 complex, alpha/beta subunit, nucleotide-binding domain, active site | 4 | $1.1 \mathrm{E}-3$ | $4.6 \mathrm{E}-2$ |
| Heat shock protein Hsp90 | 4 | $1.1 \mathrm{E}-3$ | $4.6 \mathrm{E}-2$ |

Table S5. Shared genes with retained introns as identified by Venn diagrams and KEGG pathways.

| KEGG pathway | Name | Description |
| :---: | :---: | :---: |
| Spliceosome | BUD31 | BUD31 homolog (S. cerevisiae) |
|  | DDX23 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 23 |
|  | DDX5 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 |
|  | DHX38 | DEAH (Asp-Glu-Ala-His) box polypeptide 38 |
|  | LSM4 | LSM4 homolog, U6 small nuclear RNA associated (S. cerevisiae) |
|  | LSM7 | LSM7 homolog, U6 small nuclear RNA associated (S. cerevisiae) |
|  | PRPF3 | PRP3 pre-mRNA processing factor 3 homolog (S. cerevisiae) |
|  | PRPF31 | PRP31 pre-mRNA processing factor 31 homolog (S. cerevisiae) |
|  | PRPF38B | PRP38 pre-mRNA processing factor 38 (yeast) domain containing B |
|  | PRPF8 | PRP8 pre-mRNA processing factor 8 homolog (S. cerevisiae) |
|  | RBM17 | RNA binding motif protein 17 |
|  | RBM25 | RNA binding motif protein 25 |
|  | THOC4 | THO complex 4 |
|  | U2AF1 | U2 small nuclear RNA auxiliary factor 1 |
|  | U2AF2 | U2 small nuclear RNA auxiliary factor 2 |
|  | ACIN1 | apoptotic chromatin condensation inducer 1 |
|  | CTNNBL1 | catenin, beta like 1 |
|  | EFTUD2 | elongation factor Tu GTP binding domain containing 2 |
|  | EIF4A3 | eukaryotic translation initiation factor 4A, isoform 3 |
|  | HSPA8 | heat shock 70kDa protein 8 |
|  | HNRPM | heterogeneous nuclear ribonucleoprotein M |
|  | SNRPG | hypothetical protein LOC100132425; similar to small nuclear ribonucleoprotein polypeptide G ; small nuclear ribonucleoprotein polypeptide G; small nuclear ribonucleoprotein G-like protein |
|  | PQBP1 | polyglutamine binding protein 1 |
|  | PRPF6 | similar to U5 snRNP-associated 102 kDa protein (U5-102 kDa protein); PRP6 pre-mRNA processing factor 6 homolog (S. cerevisiae) |
|  | ASCC3L1 | similar to U5 snRNP-specific protein, 200 kDa ; small nuclear ribonucleoprotein 200 kDa (U5) |


|  | WDR57 | small nuclear ribonucleoprotein 40 kDa (U5) |
| :---: | :---: | :---: |
|  | SNRPA | small nuclear ribonucleoprotein polypeptide A |
|  | SF3B14 | splicing factor 3B, 14 kDa subunit |
|  | SF3B1 | splicing factor 3 b , subunit $1,155 \mathrm{kDa}$ |
|  | SF3B2 | splicing factor 3b, subunit 2, 145kDa |
|  | SF3B3 | splicing factor 3 b , subunit $3,130 \mathrm{kDa}$ |
|  | SFRS1 | splicing factor, arginine/serine-rich 1 |
|  | SFRS2 | splicing factor, arginine/serine-rich 2 |
|  | SFRS4 | splicing factor, arginine/serine-rich 4 |
|  | SFRS5 | splicing factor, arginine/serine-rich 5 |
|  | SFRS7 | splicing factor, arginine/serine-rich 7, 35kDa |
|  | SFRS9 | splicing factor, arginine/serine-rich 9 |
|  | SART1 | squamous cell carcinoma antigen recognized by T cells |
|  | SMNDC1 | survival motor neuron domain containing 1 |
|  | TCERG1 | transcription elongation regulator 1 |
|  | TRA2A | transformer 2 alpha homolog (Drosophila) |
|  | SFRS10 | $\underline{\text { transformer } 2 \text { beta homolog (Drosophila) }}$ |
|  | USP39 | ubiquitin specific peptidase 39 |
| Huntington's disease | ATP5G3 | ATP synthase, $\mathrm{H}+$ transporting, mitochondrial F0 complex, subunit C3 (subunit |
|  |  | 9) |
|  | BAX | BCL2-associated X protein |
|  | CREBBP | CREB binding protein |
|  | NDUFA1 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa |
|  | NDUFA10 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, $10,42 \mathrm{kDa}$ |
|  | NDUFA2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa |
|  | NDUFA8 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, $8,19 \mathrm{kDa}$ |
|  | NDUFB10 | NADH dehydrogenase (ubiquinone) 1 beta subcomplex, $10,22 \mathrm{kDa}$ |
|  | NDUFS1 | NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme |
|  |  | Q reductase) |
|  | NDUFS3 | NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme |
|  |  | Q reductase) |
|  | NDUFS6 | NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme |
|  |  | Q reductase) |
|  | NDUFS7 | NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme |
|  |  | Q reductase) |


|  | NDUFV1 | NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa |
| :---: | :---: | :---: |
|  | AP2A1 | adaptor-related protein complex 2, alpha 1 subunit |
|  | AP2A2 | adaptor-related protein complex 2, alpha 2 subunit |
|  | AP2M1 | adaptor-related protein complex 2, mu 1 subunit |
|  | CLTC | clathrin, heavy chain (Hc) |
|  | CLTA | clathrin, light chain (Lca) |
|  | CLTB | clathrin, light chain (Lcb) |
|  | COX411 | cytochrome c oxidase subunit IV isoform 1 |
|  | COX7B | cytochrome c oxidase subunit Vllb |
|  | COX6B1 | cytochrome c oxidase subunit Vib polypeptide 1 (ubiquitous) |
|  | CYC1 | cytochrome c-1 |
|  | HDAC1 | histone deacetylase 1 |
|  | HDAC2 | histone deacetylase 2 |
|  | IFT57 | intraflagellar transport 57 homolog (Chlamydomonas) |
|  | POLR2A | polymerase (RNA) II (DNA directed) polypeptide A, 220kDa |
|  | POLR2B | polymerase (RNA) II (DNA directed) polypeptide B, 140kDa |
|  | POLR2E | polymerase (RNA) II (DNA directed) polypeptide E, 25kDa |
|  | POLR2F | polymerase (RNA) II (DNA directed) polypeptide F |
|  | POLR2G | polymerase (RNA) II (DNA directed) polypeptide G |
|  | POLR2H | polymerase (RNA) II (DNA directed) polypeptide H |
|  | POLR2J | polymerase (RNA) II (DNA directed) polypeptide J, 13.3kDa |
|  | NDUFS5 | similar to NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH- |
|  |  | coenzyme Q reductase): NADH dehydrogenase (ubiquinone) Fe -S protein 5 , |
|  |  | 15kDa (NADH-coenzyme Q reductase) |
|  | SLC25A5 | solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator). |
|  |  | member 5; solute carrier family 25 (mitochondrial carrier; adenine nucleotide |
|  |  | translocator), member 5 pseudogene 8 |
|  | SDHA | succinate dehydrogenase complex, subunit A, flavoprotein (Fp) |
|  | SDHB | succinate dehydrogenase complex, subunit B, iron sulfur (Ip) |
|  | SOD1 | superoxide dismutase 1, soluble |
|  | UCRC | ubiquinol-cytochrome c reductase complex ( 7.2 kD ) |
|  | UQCRC1 | ubiquinol-cytochrome c reductase core protein I |
|  | UQCRC2 | ubiquinol-cytochrome c reductase core protein II |
|  | VDAC3 | voltage-dependent anion channel 3 |
| DNA replication | MCM2 | minichromosome maintenance complex component 2 |
|  | MCM3 | minichromosome maintenance complex component 3 |
|  | MCM4 | minichromosome maintenance complex component 4 |


|  | MCM5 | minichromosome maintenance complex component 5 |
| :---: | :---: | :---: |
|  | MCM6 | minichromosome maintenance complex component 6 |
|  | MCM7 | minichromosome maintenance complex component 7 |
|  | POLD1 | polymerase (DNA directed), delta 1, catalytic subunit 125kDa |
|  | POLD2 | polymerase (DNA directed), delta 2, regulatory subunit 50kDa |
|  | POLE | polymerase (DNA directed), epsilon |
|  | POLE3 | polymerase (DNA directed), epsilon 3 (p17 subunit) |
|  | PCNA | proliferating cell nuclear antigen |
|  | RFC2 | replication factor C (activator 1) 2, 40kDa |
|  | RFC5 | replication factor C (activator 1) 5, 36.5kDa |
|  | RPA1 | replication protein $\mathrm{A1}, 70 \mathrm{kDa}$ |
|  | RPA2 | replication protein $\mathrm{A} 2,32 \mathrm{kDa}$ |
|  | RNASEH2A | ribonuclease H 2 , subunit A |
| Proteasome | PSMC3 | proteasome (prosome, macropain) 26 S subunit, ATPase, 3 |
|  | PSMD1 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 1 |
|  | PSMD11 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 11 |
|  | PSMD13 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 13 |
|  | PSMD14 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 14 |
|  | PSMD3 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 3 |
|  | PSMD7 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 7 |
|  | PSMD8 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 8 |
|  | PSME3 | proteasome (prosome, macropain) activator subunit 3 (PA28 gamma; Ki) |
|  | PSMA1 | proteasome (prosome, macropain) subunit, alpha type, 1 |
|  | PSMA5 | proteasome (prosome, macropain) subunit, alpha type, 5 |
|  | PSMA7 | proteasome (prosome, macropain) subunit, alpha type, 7 |
|  | PSMB1 | proteasome (prosome, macropain) subunit, beta type, 1 |
|  | PSMB2 | proteasome (prosome, macropain) subunit, beta type, 2 |
|  | PSMB4 | proteasome (prosome, macropain) subunit, beta type, 4 |
|  | PSMB6 | proteasome (prosome, macropain) subunit, beta type, 6 |
|  | PSMB7 | proteasome (prosome, macropain) subunit, beta type, 7 |
|  | PSMC4 | similar to 26S protease regulatory subunit 6B (MIP224) (MB67-interacting protein) (TAT-binding protein 7) (TBP-7); proteasome (prosome, macropain) $\underline{26 S \text { subunit, ATPase, } 4}$ |
| Pyrimidine metabolism | ITPA | inosine triphosphatase (nucleoside triphosphate pyrophosphatase) |


|  | NME1-NME2 | non-metastatic cells 1, protein (NM23A) expressed in; NME1-NME2 readthrough transcript; non-metastatic cells 2, protein (NM23B) expressed in |
| :---: | :---: | :---: |
|  | NME3 | non-metastatic cells 3, protein expressed in |
|  | NP | nucleoside phosphorylase |
|  | POLD1 | polymerase (DNA directed), delta 1, catalytic subunit 125kDa |
|  | POLD2 | polymerase (DNA directed), delta 2, regulatory subunit 50kDa |
|  | POLE | polymerase (DNA directed), epsilon |
|  | POLE3 | polymerase (DNA directed), epsilon 3 (p17 subunit) |
|  | POLR1A | polymerase (RNA) I polypeptide A, 194kDa |
|  | POLR1C | polymerase (RNA) I polypeptide C, 30kDa |
|  | POLR2A | polymerase (RNA) II (DNA directed) polypeptide A, 220kDa |
|  | POLR2B | polymerase (RNA) II (DNA directed) polypeptide B, 140kDa |
|  | POLR2E | polymerase (RNA) II (DNA directed) polypeptide E, 25kDa |
|  | POLR2F | polymerase (RNA) II (DNA directed) polypeptide F |
|  | POLR2G | polymerase (RNA) II (DNA directed) polypeptide G |
|  | POLR2H | polymerase (RNA) II (DNA directed) polypeptide H |
|  | POLR2J | polymerase (RNA) II (DNA directed) polypeptide J, 13.3kDa |
|  | POLR3A | polymerase (RNA) III (DNA directed) polypeptide A, 155kDa |
|  | POLR3H | polymerase (RNA) III (DNA directed) polypeptide H (22.9kD) |
|  | POLR3K | polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa |
|  | TXNRD2 | thioredoxin reductase 2 |
|  | TK1 | thymidine kinase 1, soluble |
|  | TYMS | thymidylate synthetase |
|  | UMPS | uridine monophosphate synthetase |
|  | UCK2 | uridine-cytidine kinase 2 |
| RNA polymerase | POLR1A | polymerase (RNA) I polypeptide A, 194kDa |
|  | POLR1C | polymerase (RNA) I polypeptide C, 30kDa |
|  | POLR2A | polymerase (RNA) II (DNA directed) polypeptide A, 220kDa |
|  | POLR2B | polymerase (RNA) II (DNA directed) polypeptide B, 140kDa |
|  | POLR2E | polymerase (RNA) II (DNA directed) polypeptide E, 25kDa |
|  | POLR2F | polymerase (RNA) II (DNA directed) polypeptide F |
|  | POLR2G | polymerase (RNA) II (DNA directed) polypeptide G |
|  | POLR2H | polymerase (RNA) II (DNA directed) polypeptide H |
|  | POLR2J | polymerase (RNA) II (DNA directed) polypeptide J, 13.3kDa |


|  | POLR3A | polymerase (RNA) III (DNA directed) polypeptide A, 155kDa |
| :---: | :---: | :---: |
|  | POLR3H | polymerase (RNA) III (DNA directed) polypeptide H (22.9kD) |
|  | POLR3K | polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa |
| Cell cycle | CDC45L | CDC45 cell division cycle 45-like (S. cerevisiae) |
|  | CREBBP | CREB binding protein |
|  | E2F1 | E2F transcription factor 1 |
|  | RAD21 | RAD21 homolog (S. pombe) |
|  | ANAPC5 | anaphase promoting complex subunit 5 |
|  | BUB3 | budding uninhibited by benzimidazoles 3 homolog (yeast) |
|  | CDC25A | cell division cycle 25 homolog A (S. pombe) |
|  | CCNA2 | cyclin A2 |
|  | CCNB1 | cyclin B1 |
|  | CCNB2 | cyclin B2 |
|  | CDK4 | cyclin-dependent kinase 4 |
|  | CDKN2A | cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) |
|  | HDAC1 | histone deacetylase 1 |
|  | HDAC2 | histone deacetylase 2 |
|  | MCM2 | minichromosome maintenance complex component 2 |
|  | MCM3 | minichromosome maintenance complex component 3 |
|  | MCM4 | minichromosome maintenance complex component 4 |
|  | MCM5 | minichromosome maintenance complex component 5 |
|  | MCM6 | minichromosome maintenance complex component 6 |
|  | MCM7 | minichromosome maintenance complex component 7 |
|  | PLK1 | polo-like kinase 1 (Drosophila) |
|  | PCNA | proliferating cell nuclear antigen |
|  | RBX1 | ring-box 1 |
|  | SMC1A | structural maintenance of chromosomes 1A |
|  |  | transforming |
|  | TGFB1 | growth factor, beta 1 |
| Parkinson's disease | ATP5G3 | ATP synthase, $\mathrm{H}_{+}$transporting, mitochondrial F0 complex, subunit C3 (subunit 9) |
|  | NDUFA1 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa |
|  | NDUFA10 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, $10,42 \mathrm{kDa}$ |
|  | NDUFA2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa |


|  | NDUFA8 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa |
| :---: | :---: | :---: |
|  | NDUFB10 | NADH dehydrogenase (ubiquinone) 1 beta subcomplex, $10,22 \mathrm{kDa}$ |
|  | NDUFS1 | NADH dehydrogenase (ubiquinone) Fe-S protein $1,75 \mathrm{kDa}$ (NADH-coenzyme Q reductase) |
|  | NDUFS3 | NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme Q reductase) |
|  | NDUFS6 | NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase) |
|  | NDUFS7 | NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase) |
|  | NDUFV1 | NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa |
|  | PARK7 | Parkinson disease (autosomal recessive, early onset) 7 |
|  | COX411 | cytochrome c oxidase subunit IV isoform 1 |
|  | COX7B | cytochrome c oxidase subunit Vllb |
|  | COX6B1 | cytochrome c oxidase subunit Vib polypeptide 1 (ubiquitous) |
|  | CYC1 | cytochrome c-1 |
|  | NDUFS5 | similar to NADH dehydrogenase (ubiquinone) Fe -S protein $5,15 \mathrm{kDa}$ (NADHcoenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 5 , 15 kDa (NADH-coenzyme Q reductase) |
|  | SLC25A5 | solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5; solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5 pseudogene 8 |
|  | SDHA | succinate dehydrogenase complex, subunit A, flavoprotein (Fp) |
|  | SDHB | succinate dehydrogenase complex, subunit B, iron sulfur (lp) |
|  | UCRC | ubiquinol-cytochrome c reductase complex ( 7.2 kD ) |
|  | UQCRC1 | ubiquinol-cytochrome c reductase core protein I |
|  | UQCRC2 | ubiquinol-cytochrome c reductase core protein II |
|  | $\underline{\text { UCHL1 }}$ | ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase) |
|  | UBE2G1 | ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, yeast) |
|  | UBE2G2 | ubiquitin-conjugating enzyme E2G 2 (UBC7 homolog, yeast) |
|  | VDAC3 | voltage-dependent anion channel 3 |
| Purine metabolism | ATIC | 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase |
|  | IMPDH2 | IMP (inosine monophosphate) dehydrogenase 2 |
|  | APRT | adenine phosphoribosyltransferase |
|  | AK2 | adenylate kinase 2 |
|  | HPRT1 | hypoxanthine phosphoribosyltransferase 1 |
|  | ITPA | inosine triphosphatase (nucleoside triphosphate pyrophosphatase) |


|  | NME1-NME2 | non-metastatic cells 1, protein (NM23A) expressed in; NME1-NME2 <br> readthrough transcript; non-metastatic cells 2, protein (NM23B) expressed in |
| :---: | :---: | :---: |
|  | NME3 | non-metastatic cells 3, protein expressed in |
|  | NP | nucleoside phosphorylase |
|  | NUDT5 | nudix (nucleoside diphosphate linked moiety X)-type motif 5 |
|  | PRPS1 | phosphoribosyl pyrophosphate synthetase 1; phosphoribosyl pyrophosphate synthetase 1 -like 1 |
|  | PAICS | phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase |
|  | PFAS | phosphoribosylformylglycinamidine synthase |
|  | POLD1 | polymerase (DNA directed), delta 1, catalytic subunit 125kDa |
|  | POLD2 | polymerase (DNA directed), delta 2, regulatory subunit 50kDa |
|  | POLE | polymerase (DNA directed), epsilon |
|  | POLE3 | polymerase (DNA directed), epsilon 3 (p17 subunit) |
|  | POLR1A | polymerase (RNA) I polypeptide A, 194kDa |
|  | POLR1C | polymerase (RNA) I polypeptide C, 30kDa |
|  | POLR2A | polymerase (RNA) II (DNA directed) polypeptide A, 220kDa |
|  | POLR2B | polymerase (RNA) II (DNA directed) polypeptide B, 140kDa |
|  | POLR2E | polymerase (RNA) II (DNA directed) polypeptide E, 25kDa |
|  | POLR2F | polymerase (RNA) II (DNA directed) polypeptide F |
|  | POLR2G | polymerase (RNA) II (DNA directed) polypeptide G |
|  | POLR2H | polymerase (RNA) II (DNA directed) polypeptide H |
|  | POLR2J | polymerase (RNA) II (DNA directed) polypeptide J, 13.3kDa |
|  | POLR3A | polymerase (RNA) III (DNA directed) polypeptide A, 155kDa |
|  | POLR3H | polymerase (RNA) III (DNA directed) polypeptide H (22.9kD) |
|  | POLR3K | polymerase (RNA) III (DNA directed) polypeptide K, 12.3 kDa |
|  | PKM2 | similar to Pyruvate kinase, isozymes M1/M2 (Pyruvate kinase muscle isozyme) (Cytosolic thyroid hormone-binding protein) (CTHBP) (THBP1); pyruvate kinase, muscle |
| Aminoacyl-tRNA biosynthesis | AARS | alanyl-tRNA synthetase |
|  | NARS | asparaginyl-tRNA synthetase |
|  | DARS | aspartyl-tRNA synthetase |
|  | CARS | cysteinyl-tRNA synthetase |
|  | QARS | glutaminyl-tRNA synthetase |
|  | GARS | glycyl-tRNA synthetase |
|  | LARS | leucyl-tRNA synthetase |


|  | LARS2 | leucyl-tRNA synthetase 2, mitochondrial |
| :---: | :---: | :---: |
|  | MARS | methionyl-tRNA synthetase |
|  | FARSA | phenylalanyl-tRNA synthetase, alpha subunit |
|  | FARSB | phenylalanyl-tRNA synthetase, beta subunit |
|  | SARS | seryl-tRNA synthetase |
|  | TARS | $\underline{\text { threonyl-tRNA synthetase }}$ |
|  | YARS | tyrosyl-tRNA synthetase |
| Oxidative phosphorylation | ATP5G3 | ATP synthase, $\mathrm{H}+$ transporting, mitochondrial FO complex, subunit C3 (subunit 9) |
|  | ATP51 | ATP synthase, $H_{+}$transporting, mitochondrial F0 complex, subunit E |
|  | ATP6V1G1 | ATPase, $\mathrm{H}+$ transporting, lysosomal $13 \mathrm{kDa}, \mathrm{V} 1$ subunit G1 |
|  | ATP6V1F | ATPase, $\mathrm{H}+$ transporting, Iysosomal $14 \mathrm{kDa}, \mathrm{V} 1$ subunit F |
|  | ATP6V1E1 | ATPase, $\mathrm{H}+$ transporting, lysosomal $31 \mathrm{kDa}, \mathrm{V1} \mathrm{subunit} \mathrm{E1}$ |
|  | NDUFA1 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa |
|  | NDUFA10 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42 kDa |
|  | NDUFA2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa |
|  | NDUFA8 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, $8,19 \mathrm{kDa}$ |
|  | NDUFB10 | NADH dehydrogenase (ubiquinone) 1 beta subcomplex, $10,22 \mathrm{kDa}$ |
|  | NDUFS1 | NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase) |
|  | NDUFS3 | NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme Q reductase) |
|  | NDUFS6 | NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase) |
|  | NDUFS7 | NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase) |
|  | NDUFV1 | NADH dehydrogenase (ubiquinone) flavoprotein $1,51 \mathrm{kDa}$ |
|  | COX411 | cytochrome c oxidase subunit IV isoform 1 |
|  | COX7B | cytochrome c oxidase subunit VIll |
|  | COX6B1 | cytochrome c oxidase subunit Vib polypeptide 1 (ubiquitous) |
|  | $\underline{\mathrm{CYC} 1}$ | cytochrome c-1 |
|  | NDUFS5 | similar to NADH dehydrogenase (ubiquinone) Fe -S protein $5,15 \mathrm{kDa}$ (NADHcoenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15 kDa (NADH-coenzyme Q reductase) |
|  | SDHA | succinate dehydrogenase complex, subunit A, flavoprotein (Fp) |
|  | SDHB | succinate dehydrogenase complex, subunit B, iron sulfur (lp) |
|  | UCRC | ubiquinol-cytochrome c reductase complex ( 7.2 kD ) |


|  | UQCRC1 | ubiquinol-cytochrome c reductase core protein I |
| :---: | :---: | :---: |
|  | UQCRC2 | ubiquinol-cytochrome c reductase core protein II |
| Alzheimer's disease | ATP5G3 | ATP synthase, $H+$ transporting, mitochondrial F0 complex, subunit C3 (subunit 9) |
|  | NDUFA1 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5 kDa |
|  | NDUFA10 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42 kDa |
|  | NDUFA2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8 kDa |
|  | NDUFA8 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, $8,19 \mathrm{kDa}$ |
|  | NDUFB10 | NADH dehydrogenase (ubiquinone) 1 beta subcomplex, $10,22 \mathrm{kDa}$ |
|  | NDUFS1 | NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase) |
|  | NDUFS3 | NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme Q reductase) |
|  | NDUFS6 | NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase) |
|  | NDUFS7 | NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme $\underline{Q}$ reductase) |
|  | NDUFV1 | NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa |
|  | APPBP1 | NEDD8 activating enzyme E1 subunit 1 |
|  | APP | amyloid beta (A4) precursor protein |
|  | APH1A | anterior pharynx defective 1 homolog A (C. elegans) |
|  | CALM3 | calmodulin 3 (phosphorylase kinase, delta); calmodulin 2 (phosphorylase kinase, delta); calmodulin 1 (phosphorylase kinase, delta) |
|  | CAPN2 | calpain 2, ( $\mathrm{m} / \mathrm{ll}$ ) large subunit |
|  | COX411 | cytochrome c oxidase subunit IV isoform 1 |
|  | COX7B | cytochrome c oxidase subunit VIll |
|  | COX6B1 | cytochrome c oxidase subunit Vib polypeptide 1 (ubiquitous) |
|  | CYC1 | cytochrome c-1 |
|  | HSD17B10 | hydroxysteroid (17-beta) dehydrogenase 10 |
|  | MAPK1 | mitogen-activated protein kinase 1 |
|  | NDUFS5 | similar to NADH dehydrogenase (ubiquinone) Fe -S protein 5 , 15 kDa (NADHcoenzyme Q reductase); NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15 kDa (NADH-coenzyme Q reductase) |
|  | SDHA | succinate dehydrogenase complex, subunit A, flavoprotein (Fp) |
|  | SDHB | succinate dehydrogenase complex, subunit B, iron sulfur (lp) |
|  | UCRC | ubiquinol-cytochrome c reductase complex ( 7.2 kD ) |
|  | UQCRC1 | ubiquinol-cytochrome c reductase core protein I |


|  | UQCRC2 | ubiquinol-cytochrome c reductase core protein II |
| :---: | :---: | :---: |
| Nucleotide excision repair | DDB1 | damage-specific DNA binding protein 1, 127kDa |
|  | POLD1 | polymerase (DNA directed), delta 1, catalytic subunit 125kDa |
|  | POLD2 | polymerase (DNA directed), delta 2, regulatory subunit 50kDa |
|  | POLE | polymerase (DNA directed), epsilon |
|  | POLE3 | polymerase (DNA directed), epsilon 3 (p17 subunit) |
|  | PCNA | proliferating cell nuclear antigen |
|  | RFC2 | replication factor C (activator 1) 2, 40kDa |
|  | RFC5 | replication factor C (activator 1) 5, 36.5kDa |
|  | RPA1 | replication protein $\mathrm{A1}, 70 \mathrm{kDa}$ |
|  | RPA2 | replication protein $\mathrm{A} 2,32 \mathrm{kDa}$ |
|  | RBX1 | ring-box 1 |
|  | XPC | xeroderma pigmentosum, complementation group C |
| Mismatch repair | MSH6 | mutS homolog 6 (E. coli) |
|  | POLD1 | polymerase (DNA directed), delta 1, catalytic subunit 125kDa |
|  | POLD2 | polymerase (DNA directed), delta 2, regulatory subunit 50kDa |
|  | PCNA | proliferating cell nuclear antigen |
|  | RFC2 | replication factor C (activator 1) 2, 40kDa |
|  | RFC5 | replication factor C (activator 1) 5, 36.5kDa |
|  | RPA1 | replication protein $\mathrm{A} 1,70 \mathrm{kDa}$ |
|  | RPA2 | replication protein $\mathrm{A} 2,32 \mathrm{kDa}$ |
| Citrate cycle (TCA cycle) | ACLY | ATP citrate lyase |
|  | IDH3A | isocitrate dehydrogenase 3 (NAD+) alpha |
|  | IDH3B | isocitrate dehydrogenase 3 (NAD+) beta |
|  | IDH3G | isocitrate dehydrogenase 3 (NAD+) gamma |
|  | MDH2 | malate dehydrogenase 2, NAD (mitochondrial) |
|  | PDHA1 | pyruvate dehydrogenase (lipoamide) alpha 1 |
|  | SDHA | succinate dehydrogenase complex, subunit A, flavoprotein (Fp) |
|  | SDHB | succinate dehydrogenase complex, subunit B, iron sulfur (Ip) |
|  | SUCLG1 | succinate-CoA ligase, alpha subunit |

Figure S1. MA plots per condition comparison.


Figure S2. FUS gene expression levels measured by RNA-Seq.

## FUS <br> RNA-Seq



Figure S3. FUS protein levels measured by western blot.


Figure S4. Correlation of RNA-Seq and RT-PCR for RBM25, TAF15, TARS, TPR, APP and HN1. Shown are the p-values for RNA-Seq and RT-PCR.

Differential Expression
RNA-Seq vs. RT-PCR


Figure S5. Correlation RNA-Seq and Semi-quantitative PCR for PRPF8 and RPS24. Shown are the p-values for RNA-Seq and RT-PCR.

## Exon Skipping

 RNA-Seq vs. RT-PCR

