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3 **Table 2:** TDP-43 interacting proteins found in the Nuclear/Splicing cluster. The
4 references cited here may be found in the Supplementary References.
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10 **Table 3:** TDP-43 interacting proteins found in the Cytoplasmic/Translation cluster. The
11 references cited here may be found in the Supplementary References.
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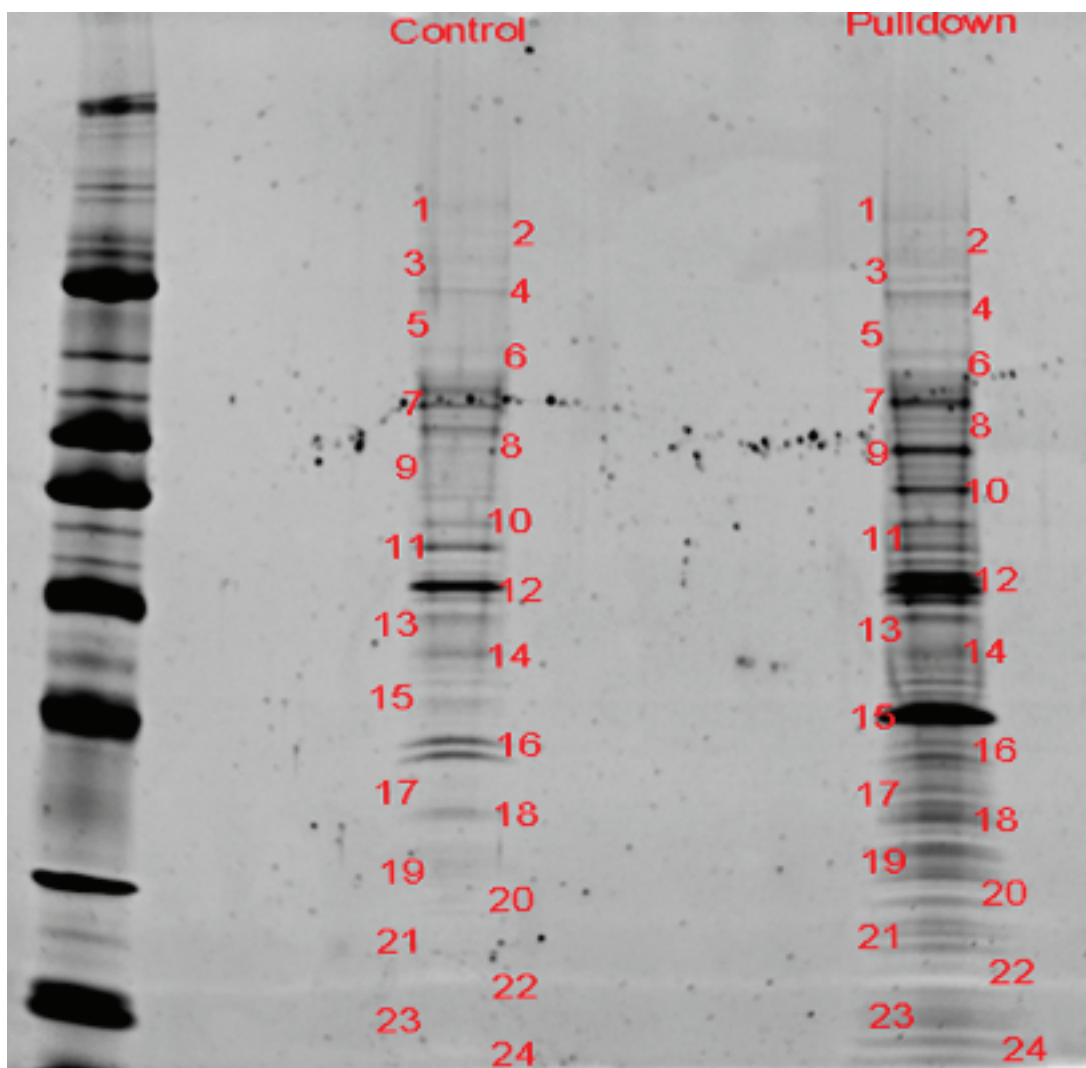
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17 **Table 4:** Stress granule proteins found to co-immunoprecipitate with TDP-43.
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22 **Supplementary Table 1:** Proteins identified by mass spectrometry that were enriched in
23 control compared to TDP-43 immunoprecipitation. A pound symbol (#) in the final
24 column indicates the protein was only present in the control lane.
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31 **Supplementary Figure 1:** The image shows the location of bands analyzed by mass
32 spectrometry.
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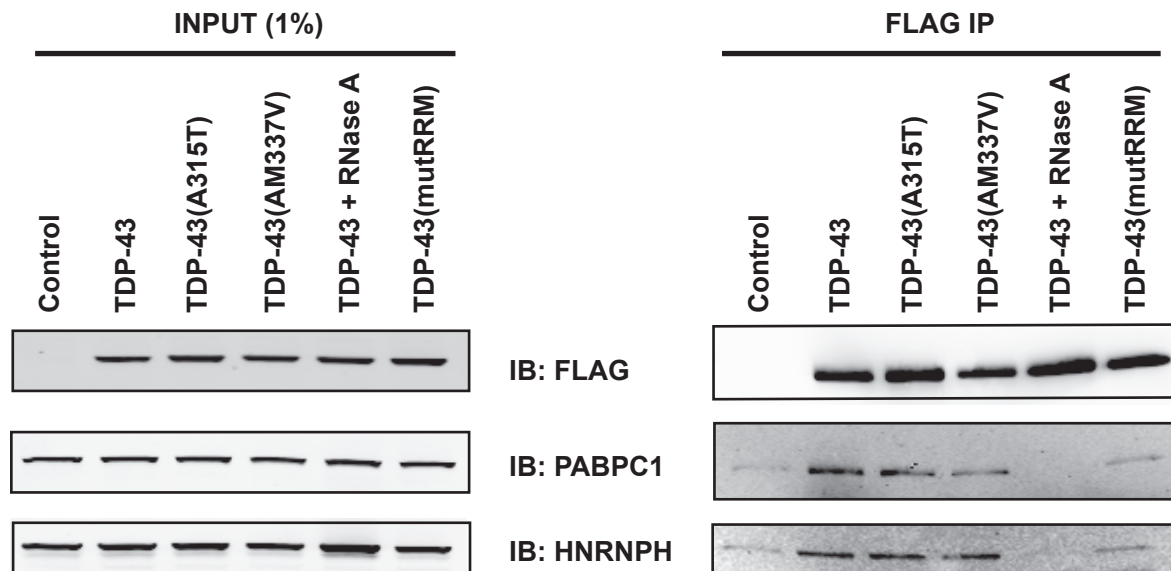
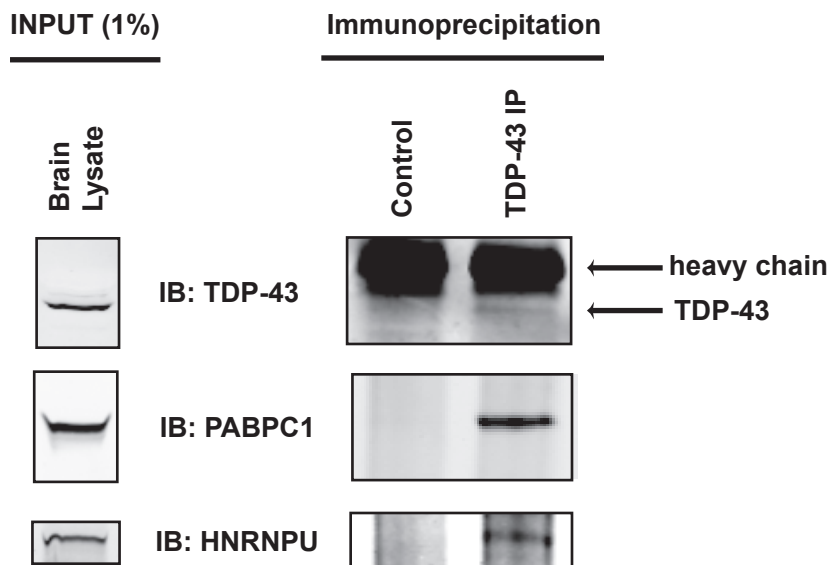
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38 **Supplementary Figure 2: Validation of Interactions in HeLa cells and mouse brain**
39 **homogenate.** (A) Validation of TDP-43 interaction with hnRNP H and PABPC1 by co-
40 immunoprecipitation followed by Western blot analysis in HeLa cells. Left panel:
41 Western blot analysis of whole cell lysates prior to immunoprecipitation was used to
42 visualize 1% of protein input. Right panel: Western blot analysis of FLAG
43 immunoprecipitates. (B) Validation of TDP-43 interaction with PABPC1 and hnRNP U
44 in mouse brain. Left Panel: Western blot analysis of mouse brain lysates prior to
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3 immunoprecipitation was used to visualize 1% of protein input. Right Panel: Western
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5 blot analysis of endogenous TDP-43 immunoprecipitates.
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Supplementary Figure 1: The image shows the location of bands analyzed by mass spectrometry.

A**B**

Supplementary Figure 2: Validation of Interactions in HeLa cells and mouse brain (A) Validation of TDP-43 interaction with hnRNP H and PABPC1 by co-immunoprecipitation followed by Western blot analysis in HeLa cells. Left panel: Western blot analysis of whole cell lysates prior to immunoprecipitation was used to visualize 1% of protein input. Right panel: Western blot analysis of FLAG immunoprecipitates. **(B)** Validation of TDP-43 interaction with PABPC1 and hnRNP U in mouse brain. Left Panel: Western blot analysis of mouse brain lysates prior to immunoprecipitation was used to visualize 1% of protein input. Right Panel: Western blot analysis of endogenous TDP-43 immunoprecipitates.

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3 **Supplementary Table 1: Proteins enriched in control lane**

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Protein Name	Symbol	Molecular Weight (kDa)	Accession Number	Total Spectra: FLAG IP	Unique Peptides: FLAG IP	Percent Coverage: FLAG IP	Total Spectra: Control	Unique Peptides: Control	Percent Coverage: Control	Ratio: IP / Control
Kinesin-like protein KIF11	KIF11	119	P52732	47	24	27	50	30	28	0.9
Leucine-rich PPR motif-containing protein, mitochondrial	LRPPRC	158	P42704	39	23	17	63	43	32	0.6
Protein arginine N-methyltransferase 5	PRMT5	73	O14744	37	15	27	50	14	22	0.7
RNA-binding protein 10	RBM10	104	P98175	36	14	15	41	18	21	0.9
Actin, cytoplasmic 1	ACTB	42	P60709	29	12	33	47	10	33	0.6
Thyroid hormone receptor-associated protein 3	THRAP3	109	Q9Y2W1	21	12	13	52	13	12	0.4
26S proteasome non-ATPase regulatory subunit 1	PSMD1	106	Q99460	20	2	2	20	1	1	1.0
Protein phosphatase 1B	PPM1B	53	O75688	18	7	17	21	10	27	0.9
Heat shock protein HSP 90-beta	HSP90AB1	83	P08238	16	8	13	21	7	11	0.8
Splicing factor 3B subunit 3	SF3B3	136	Q15393	15	12	12	23	12	13	0.7
Glyceraldehyde-3-phosphate dehydrogenase	GAPDH	36	P04406	13	3	14	27	5	24	0.5
General transcription factor II-I	GTF2I	112	P78347	11	9	12	13	10	11	0.8
Histone H2A type 1-B/E	HIST1H2AB	14	P04908	10	3	27	22	1	7	0.5
Small nuclear ribonucleoprotein-associated proteins B and B'	SNRPB	25	P14678	10	3	13	26	6	25	0.4
40S ribosomal protein S8	RPS8	24	P62241	9	5	23	9	3	19	1.0
Serine/threonine-protein kinase RIO1	RIOK1	66	Q9BRS2	9	5	9	10	6	11	0.9
Elongation factor 1-alpha 1	EEF1A1	50	P68104	9	3	7	11	3	6	0.8
Eukaryotic translation initiation factor 4B	EIF4B	69	P23588	9	4	6	15	6	9	0.6
Stress-70 protein, mitochondrial	HSPA9	74	P38646	8	5	9	8	5	10	1.0
Methylosome protein 50	WDR77	37	Q9BQA1	8	6	27	11	7	18	0.7
Replication protein A 70 kDa DNA-binding subunit	RPA1	68	P27694	8	6	7	18	11	17	0.4
Peroxisiredoxin-1	PRDX1	22	Q06830	6	4	20	6	3	16	1.0
Putative pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15	DHX15	91	O43143	6	3	5	6	3	5	1.0
Histone H4	HIST1H4A	11	P62805	6	2	21	7	1	10	0.9
Protein arginine N-methyltransferase 1	PRMT1	42	Q99873	6	4	9	7	6	17	0.9
Splicing factor 3B subunit 2	SF3B2	98	Q13435	6	4	4	11	8	8	0.5
Bcl-2-associated transcription factor 1	BCLAF1	106	Q9NYF8	6	3	4	19	12	14	0.3
L-lactate dehydrogenase B chain	LDHB	37	P07195	5	5	17	7	5	17	0.7
U4/U6 small nuclear ribonucleoprotein Prp31	PRPF31	55	Q8WWY3	5	3	7	7	4	9	0.7
L-lactate dehydrogenase A chain	LDHA	37	P00338	4	2	6	4	2	6	1.0
Protein unc-84 homolog B	UNC84B	80	Q2T9F7	4	2	2	4	3	5	1.0
Calmodulin-regulated spectrin-associated protein 3	KIAA1543	135	Q9P1Y5	4	3	3	5	4	4	0.8
Peptidyl-prolyl cis-trans isomerase A	PPIA	18	P62937	4	2	12	5	4	19	0.8
Phosphoribosyl pyrophosphate synthetase-associated protein 2	PRPSAP2	41	O60256	4	2	6	5	3	10	0.8
Histone H2B type 1-D	HIST1H2BD	14	P58876	4	3	24	7	2	19	0.6
40S ribosomal protein S15a	RPS15A	15	P62244	3	1	7	3	2	13	1.0
ATP synthase subunit beta, mitochondrial	ATP5B	57	P06576	3	2	4	3	2	5	1.0
Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase, mitochondrial	MTHFD2	38	B8ZZU9	3	2	7	3	2	7	1.0
KH domain-containing, RNA-binding, signal transduction-associated protein 1	KHDRBS1	48	Q07666	3	2	5	3	2	4	1.0

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Protein Name	Symbol	Molecular Weight (kDa)	Accession Number	Total Spectra: FLAG IP	Unique Peptides: FLAG IP	Percent Coverage: FLAG IP	Total Spectra: Control	Unique Peptides: Control	Percent Coverage: Control	Ratio: IP / Control
Single-stranded DNA-binding protein, mitochondrial	SSBP1	17	Q04837	3	1	5	3	2	16	1.0
Spindlin-1	SPIN1	30	Q9Y657	3	2	9	3	1	4	1.0
Splicing factor 3 subunit 1	SF3A1	89	Q15459	3	3	5	3	3	5	1.0
Pyruvate kinase isozymes M1/M2	PKM2	58	P14618	3	2	4	5	3	6	0.6
Spectrin beta chain, brain 1	SPTBN1	275	Q01082	3	3	2	5	5	2	0.6
14-3-3 protein epsilon	YWHAE	29	P62258	2	2	9	2	1	5	1.0
Ribose-phosphate pyrophosphokinase 1	PRPS1	35	P60891	2	2	8	2	1	4	1.0
Fragile X mental retardation syndrome-related protein 2	FXR2	74	P51116	2	1	3	4	3	4	0.5
Heat shock protein HSP 90-alpha	HSP90AA1	85	P07900	2	1	2	4	3	5	0.5
Replication protein A 32 kDa subunit	RPA2	29	P15927	2	2	7	4	3	13	0.5
Serine/threonine-protein kinase 38-like	STK38L	54	Q9Y2H1	2	2	5	4	2	6	0.5
Small nuclear ribonucleoprotein Sm D3	SNRPD3	14	P62318	2	1	7	4	2	15	0.5
Coproporphyrinogen-III oxidase, mitochondrial	CPOX	50	P36551	2	2	4	5	3	8	0.4
Splicing factor 3B subunit 1	SF3B1	146	O75533	2	2	2	7	6	5	0.3
Ribose-phosphate pyrophosphokinase 2	PRPS2	35	P11908	2	2	6	9	6	22	0.2
OTU domain-containing protein 4	OTUD4	124	Q01804	2	1	1	21	10	13	0.1
F-actin-capping protein subunit alpha-1	CAPZA1	33	P52907	1	1	5	2	2	11	0.5
T-complex protein 1 subunit theta	CCT8	60	P50990	1	1	2	2	2	4	0.5
Serine/arginine repetitive matrix protein 2	SRRM2	300	Q9UQ35	1	1	1	4	3	1	0.3
Calcium homeostasis endoplasmic reticulum protein	CHERP	104	Q8IWX8	1	1	1	6	4	5	0.2
Protein quaking	QKI	38	Q96PU8	1	1	2	6	3	11	0.2
Spectrin alpha chain, brain	SPTAN1	285	Q13813	1	1	0	6	6	4	0.2
14-3-3 protein zeta/delta	YWHAZ	28	P63104	0	0	0	2	2	11	#
CCR4-NOT transcription complex subunit 1	CNOT1	267	A5YKK6	0	0	0	2	2	1	#
Kanadaplin	SLC4A1AP	89	Q9BWU0	0	0	0	2	2	3	#
Phosphoribosyl pyrophosphate synthetase-associated protein 1	PRPSAP1	39	Q14558	0	0	0	2	2	8	#
RB1-inducible coiled-coil protein 1	RB1CC1	183	Q8TDY2	0	0	0	2	2	2	#
Alpha-enolase	ENO1	47	P06733	0	0	0	4	3	6	#
U7 snRNA-associated Sm-like protein LSM11	LSM11	40	P83369	0	0	0	5	4	13	#

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