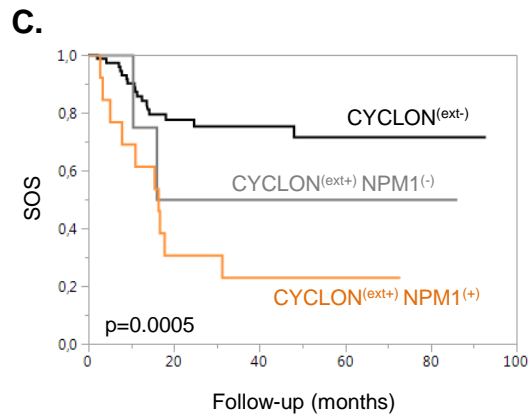
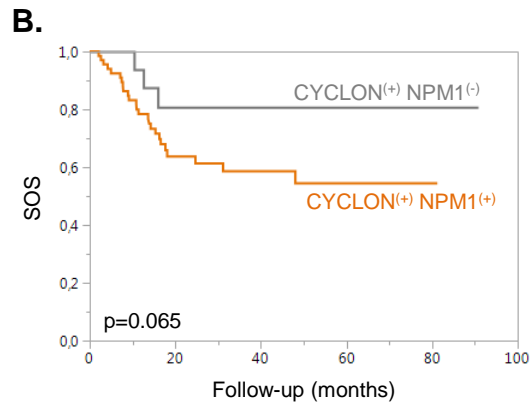
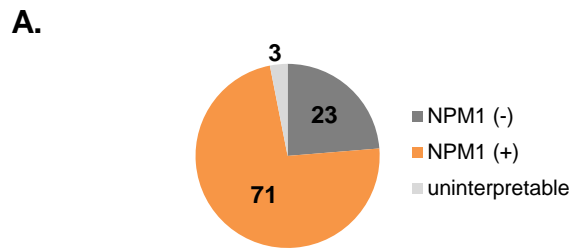
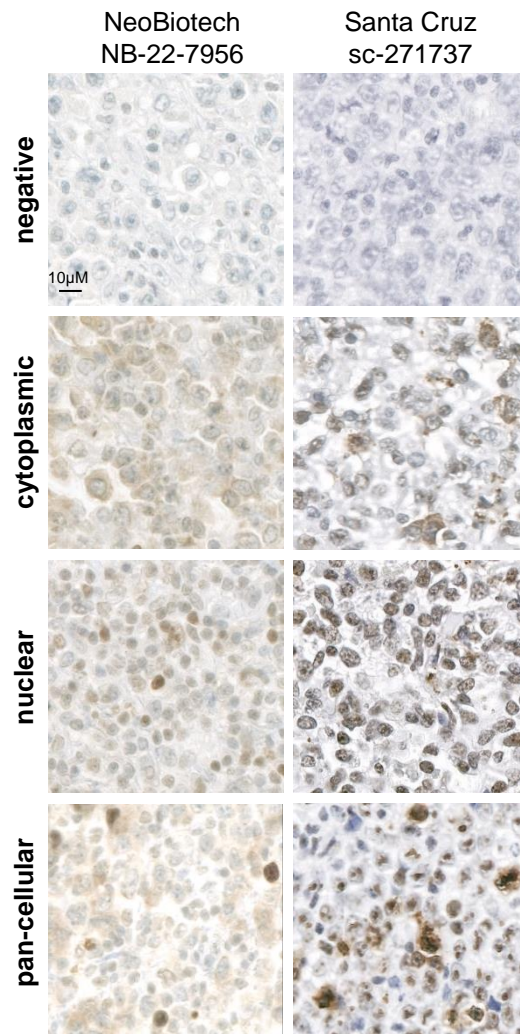


**Figure S1: Experimental approach for identification of CYCLON protein-protein interaction network in B593 DLBCL cell line.** **A.** Immunoblot analysis of B593 mock and GFP-CYCLON cells using anti-GFP and anti-CYCLON antibody. **B.** Agarose gel electrophoresis showing nucleic acids profiles before (-) and after (+) MNase digestion used to solubilize CYCLON-associated complexes. **C.** Western blot analysis of CYCLON and CYCLON-GFP in input, flow-through (FT, eq 1 volume) and GFP-Trap immunoprecipitated (IP, eq. 10 volumes) fractions as indicated. **D.** Representative silver staining of the GFP-Trap immunoprecipitated fraction in B593 mock and GFP-CYCLON cell lines.

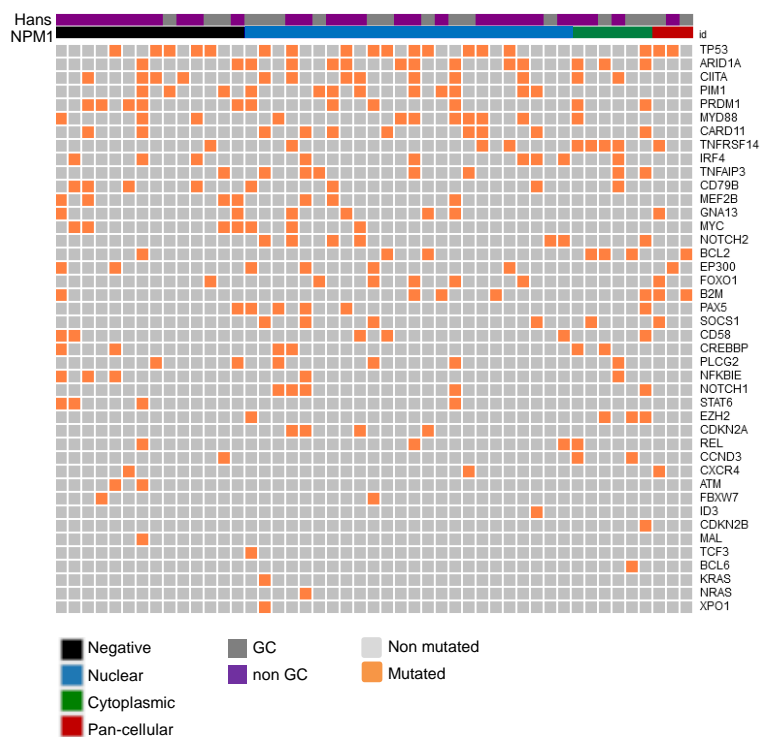


**Figure S2: NPM1 IHC evaluation in DLBCL reveals an association of CYCLON/NPM1 double positivity with prognosis.** **A.** Pie-chart representation of NPM1 positivity determined by IHC staining in a DLBCL cohort (n=97). **B.** Kaplan-Meier analysis of SOS associated with CYCLON single expressor (CYCLON<sup>(+)</sup> NPM1<sup>(-)</sup>) or CYCLON/NPM1 double expressors (CYCLON<sup>(+)</sup> NPM1<sup>(+)</sup>). **C.** Kaplan-Meier analysis of SOS associated with CYCLON non extra-nucleolar (CYCLON<sup>(ext-)</sup>), CYCLON extra-nucleolar pattern/NPM1 negative (CYCLON<sup>(ext+)</sup> NPM1<sup>(-)</sup>) or CYCLON extra-nucleolar pattern/NPM1 double expressors (CYCLON<sup>(ext+)</sup> NPM1<sup>(+)</sup>). p values are derived from a log rank test.

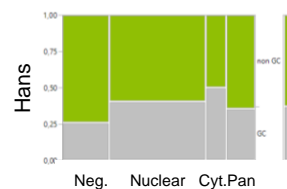


**Figure S3. Validation of NPM1 staining patterns using an alternative antibody.** IHC analysis performed on 26 DLBCL cases using 2 distinct mouse monoclonal antibodies (NeoBiotech clone 7H10B9 #NB-22-7956 and Santa Cruz #sc-271737) gave similar results, confirming the validity of NPM1 alternative localizations in DLBCL. Four representative cases are presented.

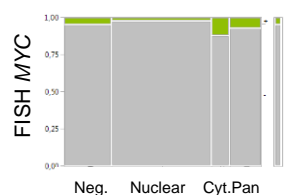
**A.**



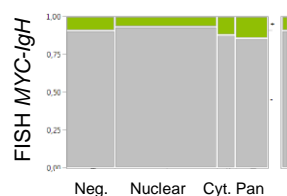
**B.**



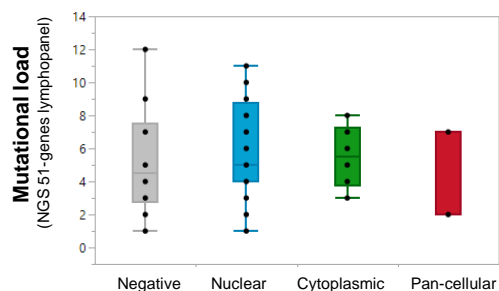
**C.**



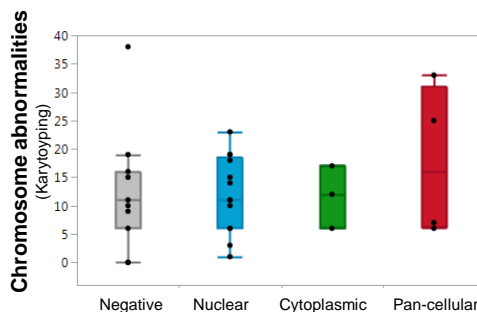
**D.**



**E.**

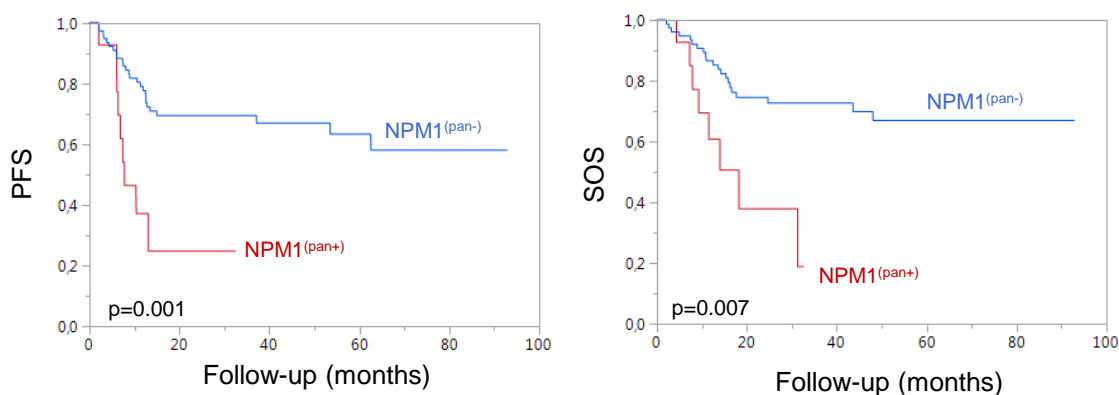


**F.**

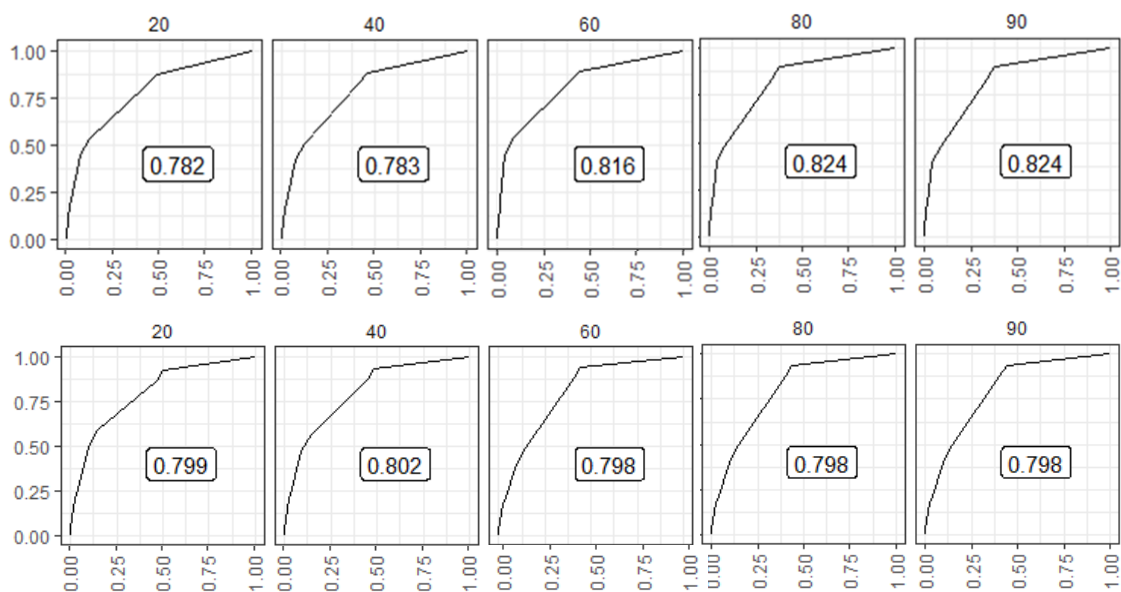


**Figure S4. Investigation of genetic abnormalities according to NPM1 staining patterns.** **A.** Heatmap representation of mutational profiles derived from NGS targeted sequencing (n=48) including 51 genes sorted by mutation frequency as indicated. **B-D.** Mosaic plots between NPM1 staining pattern and Hans non-GC/GC classification (B, n=97), *MYC* rearrangement (C, n=87), *MYC-IgH* rearrangement (D, n=87). **E-F.** Boxplot representation of mutational load (E, n=47) and number of chromosome abnormalities (F, n=38) for each NPM1 staining patterns.

**A.**



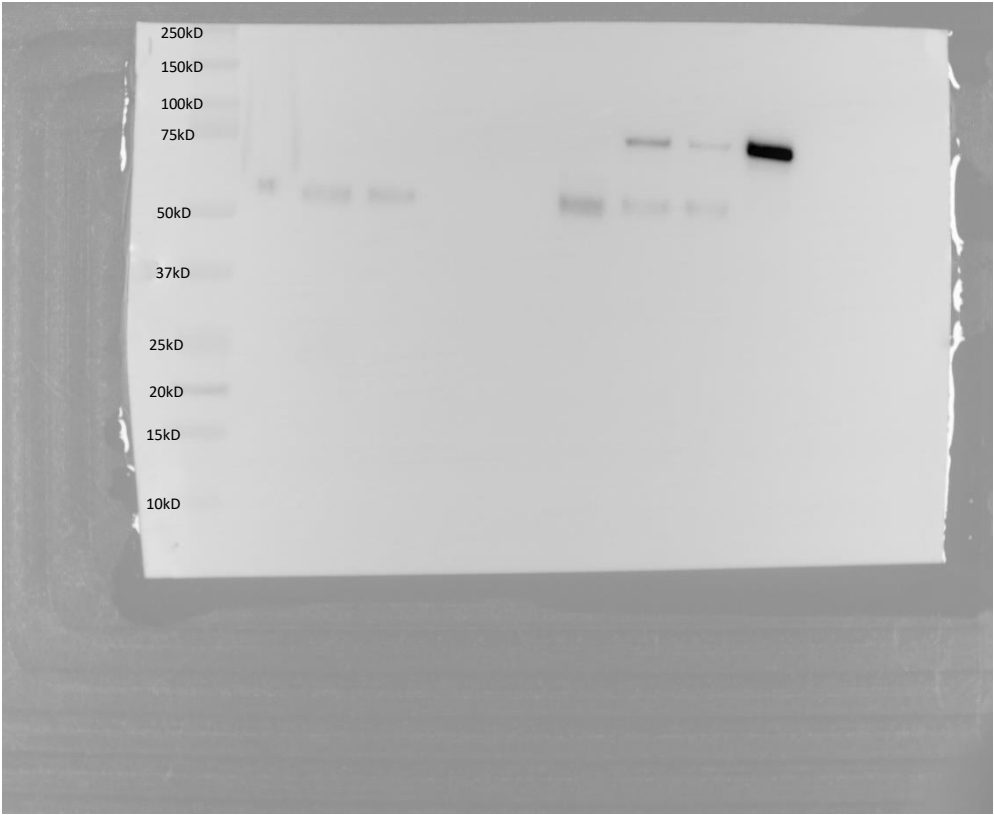
**B.**



**Figure S5: NPM1 pan-cellular staining (NPM1<sup>(pan+)</sup>) defines a very poor prognosis group among DLBCL patients.** **A.** Kaplan-Meier analyses of PFS (left) and SOS (right) associated with pan-cellular NPM1 staining (NPM1<sup>(pan+)</sup>) and non pan-cellular NPM1 staining (NPM1<sup>(pan-)</sup>). **B.** Time-dependent receiver operating characteristic (ROC) curves evaluating prediction accuracy of multivariate bootstrap Cox regression analysis of NPM1, CYCLON and R-IPI (Table 2) over time (20, 40, 60, 80 and 90 months as indicated). x axis: false positive rate, y axis: true positive rate. Box: area under the curve (AUC) for multivariate PFS (upper panel) and OS (lower panel) models.

Original\_western\_blot

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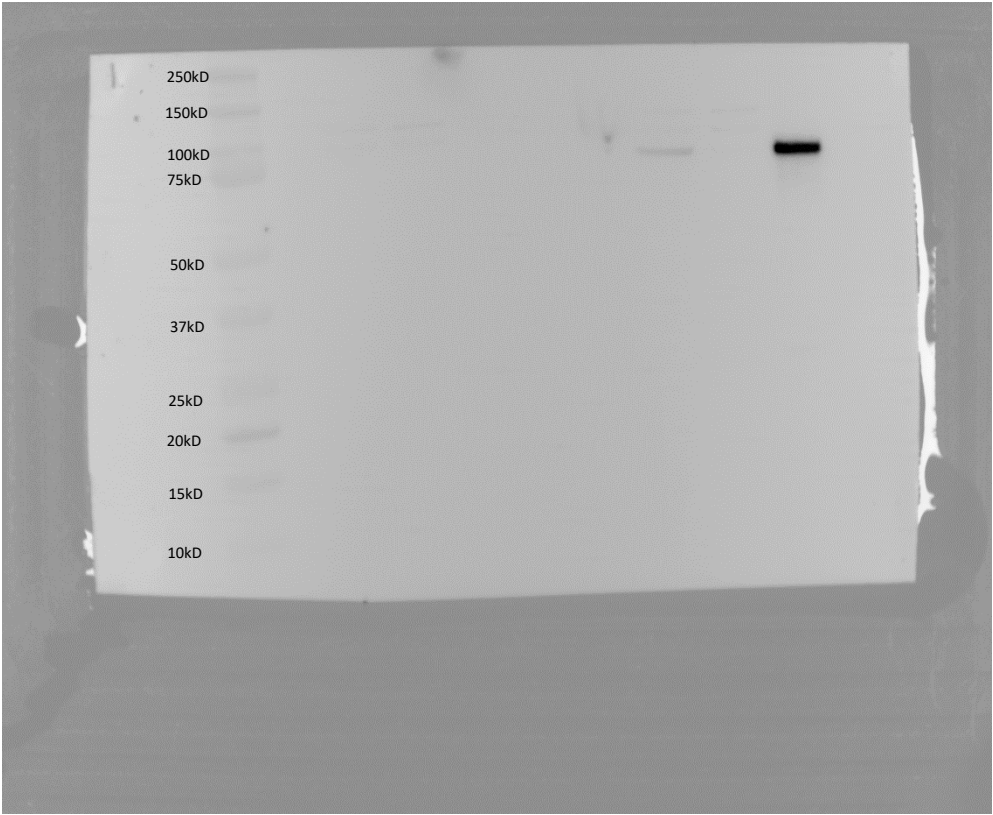


Table S1 : CYCLON interactome in B593 cells

This table lists proteins found significantly more abundant (log<sub>2</sub>(Fold Change) ≥ 1.5 ; p-value ≤ 0.05) in eluates from GFP-Cyclon compared to control immunoprecipitations.

accession	protein name	gene name	Mol. Weight	Identified peptides	coverage (%)	log <sub>2</sub> (Fold Change CYCLON/CTL)	p-value	abundance CTL1	abundance CTL2	abundance CTL3	abundance Cyclon1	abundance Cyclon2	abundance Cyclon3
CCD86_HUMAN	Coiled-coil domain-containing protein 86	CCDC86	40236	21	50.28	11.57	2.61E-08	14.84335724	14.85226645	14.71945751	26.82049972	27.02233966	25.27892001
B1B1J6_HUMAN	Chemokine-like protein TAF4-5 (Fragment)	TAF45	19689	1	4.97	7.15	4.20E-04	14.84335724	14.85226645	14.71945751	24.6809757	22.87983925	18.29600344
DHX9_HUMAN	ATP-dependent RNA helicase A	DHX9	140958	32	24.65	6.52	1.12E-04	19.05211055	19.31978048	20.0429251	28.53570988	24.97127383	24.47450116
B3KTW4_HUMAN	cDNA FLJ38868 fis, clone MESAN2013211, highly similar to Protein FAM98A	FAM98A	37260	1	2.25	5.58	1.14E-03	14.84335724	14.85226645	14.71945751	22.71550264	21.24375906	17.20094317
Q59EC0_HUMAN	Adenosine deaminase, RNA-specific isoform ADAR-a variant (Fragment)	DSRAD	137833	21	17.68	5.51	9.47E-04	19.23409719	15.33922293	18.67450145	25.20755392	22.27234265	22.29081667
ALBUJ_HUMAN	Serum albumin	ALB*	69367	18	25.62	5.40	1.19E-03	21.8966324	21.40461257	23.72059441	29.87569185	28.29568509	25.04383951
U2AFM_HUMAN	U2 small nuclear ribonucleoprotein auxiliary factor 35 kDa subunit-related protein 2	ZRSR2	58045	1	1.66	4.98	1.45E-04	14.84335724	14.85226645	14.71945751	20.91474523	20.26520537	18.17025965
RT22_HUMAN	28S ribosomal protein S22, mitochondrial	MRPS22	41280	4	9.17	4.92	2.81E-04	15.0717662	15.4782971	14.53293325	18.30176323	21.55375815	19.9767098
ROAO_HUMAN	Heterogeneous nuclear ribonucleoprotein A0	HNRNPA0	30841	1	5.57	4.56	9.44E-05	14.84335724	14.85226645	14.71945751	19.05011822	18.66801153	20.37442415
5NT1B_HUMAN	Cytosolic 5'-nucleotidase 1B	NT5C1B	68804	1	1.31	4.49	3.49E-02	14.84335724	14.85226645	14.71945751	22.82586426	21.06170345	14.00296406
TRIM5_HUMAN	Tripartite motif-containing protein 5	TRIM5	56338	1	1.42	4.11	1.13E-03	16.0500409	17.5703621	16.14148191	21.5901322	21.53946827	18.95034607
ILF3_HUMAN	Interleukin enhancer-binding factor 3	ILF3	95338	8	8.28	3.62	5.89E-03	18.30047604	18.05094648	17.15730549	23.83979558	19.78927529	20.73779232
PTCD3_HUMAN	Pentatricopeptide repeat domain-containing protein 3, mitochondrial	PTCD3	78550	2	2.61	3.49	2.94E-03	14.84335724	14.85226645	14.71945751	16.40070981	19.55047175	18.9320219
RALY_HUMAN	RNA-binding protein Raly	RALY	32463	2	5.56	3.27	1.84E-03	16.86690815	14.96208474	17.10159095	19.72018243	19.42733062	19.60235327
NCOA5_HUMAN	Nuclear receptor coactivator 5	NCOA5	65536	4	7.43	3.25	1.25E-02	18.00318141	17.58127188	14.70730157	21.67939816	19.34718217	19.00977799
SSBP_HUMAN	Single-stranded DNA-binding protein, mitochondrial	SSBP1	17260	3	21.62	2.95	3.54E-03	16.94688099	18.60620875	16.77132937	20.97500645	20.43971944	19.76546454
RL11_HUMAN	60S ribosomal protein L11	RPL11	20252	3	16.29	2.78	4.29E-03	18.32091105	17.12476226	18.79563625	21.59057075	20.51693802	20.47023662
HNRH2_HUMAN	Heterogeneous nuclear ribonucleoprotein H2	HNRNPH2	49264	5	14.25	2.73	3.06E-02	20.44923474	16.94117843	20.91502763	21.94169259	23.21112773	21.35494349
CSK21_HUMAN	Casein kinase II subunit alpha	CSNK2A1	45144	1	1.79	2.73	7.12E-03	13.84558736	14.21696396	13.34713151	17.96307582	15.9428699	15.68340796
CHAP1_HUMAN	Chromosome alignment-maintaining phosphoprotein 1	CHAMP1	89099	4	5.67	2.49	4.20E-02	17.89212686	17.36651422	16.99545351	22.51099737	18.70766506	18.4938012
NPM_HUMAN	Nucleophosmin	NPM1	32575	11	40.82	2.41	4.05E-02	22.97270302	19.58807703	22.55617841	25.38420401	23.30362209	23.65071285
YLP1M1_HUMAN	YLP motif-containing protein 1	YLP1M1	219985	3	2.41	2.41	1.87E-02	16.99543643	16.93687184	16.92424308	20.74003865	17.70314188	19.63437325
HNRPC_HUMAN	Heterogeneous nuclear ribonucleoproteins C1/C2	HNRNPC	33670	9	27.12	2.37	8.08E-03	21.8359899	20.93343331	22.33927475	23.93934899	23.65740443	24.63047657
HNRH3_HUMAN	Heterogeneous nuclear ribonucleoprotein H3	HNRNPH3	36926	6	19.08	2.34	4.92E-02	19.36035324	16.68450736	20.58117744	20.57301908	20.69349127	22.3880408
RM38_HUMAN	39S ribosomal protein L38, mitochondrial	MRPL38	44597	1	2.63	2.24	1.75E-02	14.84335724	14.85226645	14.71945751	15.85904084	18.30247299	16.96138363
RM50_HUMAN	39S ribosomal protein L50, mitochondrial	MRPL50	18325	2	15.19	2.18	1.57E-02	15.8967047	16.32832488	15.33480242	17.41321501	19.09088203	17.59929303
KHDR1_HUMAN	KH domain-containing, RNA-binding, signal transduction-associated protein 1	KHDRBS1	48227	2	5.42	2.13	1.81E-02	18.5462055	16.55495408	16.96493023	19.72022887	19.41293331	19.33193009
RT27_HUMAN	28S ribosomal protein S27, mitochondrial	MRPS27	47611	2	4.83	2.09	3.01E-02	18.24532131	16.15215068	17.77884251	18.54859064	20.3131386	19.59284667
NH2L1_HUMAN	NHP2-like protein 1	SNU13	14174	3	25	2.04	3.25E-02	17.55394951	16.21566771	17.42564215	20.04557047	17.78512403	19.49181917
RS14_HUMAN	40S ribosomal protein S14	RPS14	16273	2	15.89	1.97	4.30E-02	16.48732461	17.70212005	15.86502747	17.72218187	19.97174659	18.26068276
MATR3_HUMAN	Matrin-3	MATR3	94623	6	6.38	1.95	1.88E-02	19.95500585	18.61726312	19.27685771	21.25401284	21.45519384	20.97852671
HNRPU_HUMAN	Heterogeneous nuclear ribonucleoprotein U	HNRNPU	90584	4	5.82	1.84	2.13E-02	16.6066174	15.86923338	16.74380347	18.48122202	17.96977138	18.3454814
ARHGH_HUMAN	Rho guanine nucleotide exchange factor 17	ARHGEF17	221673	1	0.39	1.79	4.14E-02	18.69410592	18.81672094	17.76979465	20.82974159	20.69417241	19.11284309
IF4A3_HUMAN	Eukaryotic initiation factor 4A-III	EIF4A3	46871	4	8.52	1.73	3.70E-02	17.01552631	17.9476555	18.14697472	18.99669479	19.15455293	20.14176801

Legend :

- imputed values for values totally missing in the condition
- imputed value for partially missing value in the condition

\*ALB was excluded from the final list for graphical representation and ontology analysis as a very likely contaminant protein