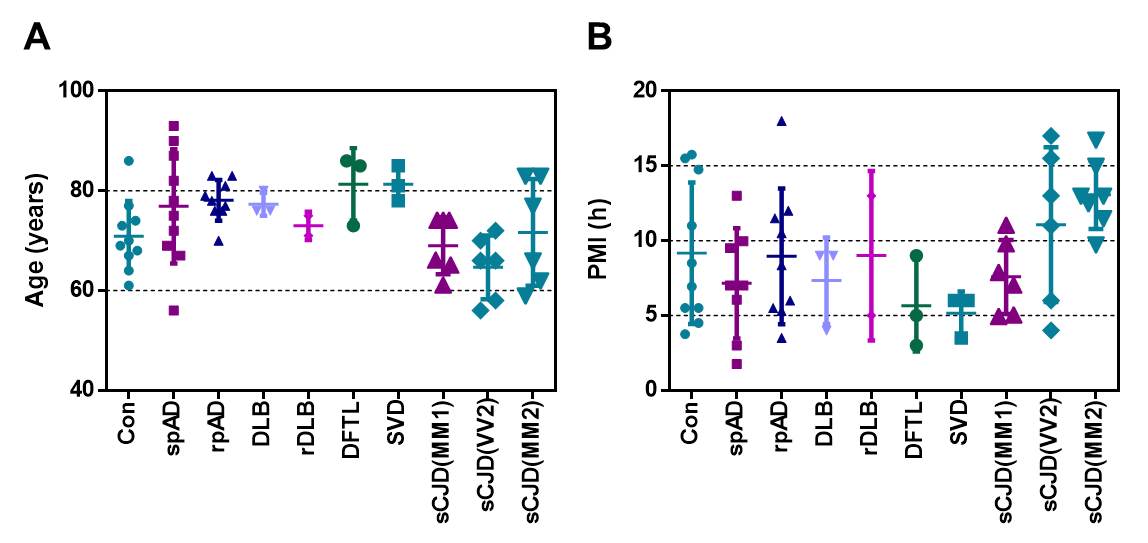
# SUPPLEMENTARY figures and tables

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Suppl. figure 1: Summary of frontal cortex cohorts used in current study. Further clinical features and neuropathological details of the cohort are given in the Additional file 2.



Suppl. figure 2: Sample cohorts used in the study A) Comparison of ages of the diverse pathological groups used in the study. B) Graph presents a comparison of post-mortem intervals to the time of autopsies.

Suppl. table 1 : List of primary antibodies and their applications in the current study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Primary Antibody** | **Origin** | **Dilution (IB/IP)** | **Dilution (IF)** | **Company/ Cat. No.** |
| SAF 70 (anti PrP antibody) | Mouse IgG2b | 1:1000/1:100 | 1:100 | SPIbio / A03206 |
| Actin-beta | Mouse IgM | 1:10000 | 1:100 | Sigma / A5441 |
| Zinc Alpha 2 Glycoprotein | Mouse IgG1 | 1:1000/ 1:100 | 1:100 | Abcam / ab117275 |
| GAPDH | Mouse IgM | 1:10000 | - | Sigma / G8795 |
| G2L2 | Rabbit IgG | 1:1000 | 1:100 | Abcam / ab170275 |
| EB-1 | Rabbit IgG | 1:1000 | 1:100 | Invitrogen / PA5-25913 |
| Tubulin-alpha | Mouse IgG | 1:1000 | 1:100 | Santacruz biotech. / sc-58667 |

Suppl. table 2: List of secondary antibodies and their applications in current study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Secondary antibody** | **Origin** | **Dilution (IB)** | **Dilution (IF)** | **Company/ Cat. No.** |
| α-Mouse-HRP | Goat | 1:10000 | - | JacksonIR Lab / 115-035-062 |
| α-Rabbit-HRP | Goat | 1:10000 | - | JacksonIR Lab / 111-035-144 |
| α-Goat-HRP | Goat | - | 1:200 | JacksonIR Lab / 705-035-003 |
| α-Mouse-A488 | Goat | - | 1:200 | Thermo Fischer Sci. / A32723 |
| α-Rabbit-A488 | Goat | - | 1:200 | Thermo Fischer Sci. / A-11034 |
| α-Mouse-A546 | Goat | - | 1:200 | Thermo Fischer Sci. / A-11003 |
| α-Rabbit-A546 | Goat | - | 1:200 | Thermo Fischer Sci. / A-11010 |

**High density prion protein interactors in spAD and sCJD**

Nine common interactors between CJD-MM1 and spAD HDFs, likewise, we could also identify three interactors common to the controls and spAD HDFs including cathepsin D (CTSD), catenin beta-1 (CTNNB1) and protein piccolo (PCLO). However, as HDPs are not reported previously for the Con and spAD, the HDP interacting proteins could be detected in Co-IP eluates from spAD and Con HDFs because of unspecific binding to Dynabeads. Nineteen common interactors for CJD-MM2 HDPs and seven from that of sCJD-VV2 were found in spAD-HDFs as well. The number of HDP-interactors for the sCJD-subtypes was higher compared to that of controls, spAD and rpAD and the degree of intergroup overlap between the HDP-interactors from sCJD subtypes was also the highest, presumably due to pathological similarities among the prion strains (**additional file 7**). Aldolase c was commonly identified between HDPs of spAD and VV2. Catenin beta-1 and aconitase hydratase were commonly present between the spAD, VV2 and MM2 HDFs. Three proteins, namely protein piccolo, cathepsin D and triosephosphate isomerase were found commonly interacting to HDPs between the HDFs of spAD, CJD-MM1, CJD-VV2 and CJD-MM2 (**additional file 7**).

Three proteins including calmodulin-like protein 5, endoplasmin and malate dehydrogenase, mitochondrial, were found in the HDFs of spAD, CJD-MM1 and CJD-MM2. Three HDP-interactors, antileukoproteinase, amyloid precursor proteins and 14-3-3E were found in the HDFs from sCJD-MM1 and sCJD-MM2 subtypes (Suppl. figure 3). The high density PrP interactors commonly expressed in all sCJD-subtypes are listed below along-with their disease relevance, and corresponding HDFs (Suppl. table 3).

Suppl. table 3: High-density PrP (HDP) interactors commonly found in the HDFs of all sCJD subtypes.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene IDs** | **Uniprot Acc. No.** | **Identified Proteins** | **Subcellular location** | **Prion protein-interaction** | **Involvement in disease** | **HDFs-Occurrence** |
| **TPP1** | O14773 | Tripeptidyl-peptidase 1 | Ly | Novel | Ceroid lipofuscinosis, neuronal, 2 [38] | sCJD-MM1:F12 toF14,  sCJD-MM2:F12 toF14, F16, F17  sCJD-VV2:F14 |
| **FRIH** | P02794 | Ferritin heavy chain |  | Known [25] | Creutzfeldt-Jakob-disease [25]5 | sCJD-MM1:F12 toF14,  sCJD-MM2:F12, F13,  sCJD-VV2:F12, F13 |
| **EPDR1** | Q9UM22 | Mammalian ependymin-related protein 1 | S | Novel |  | sCJD-MM1:F13 to F16,  sCJD-MM2:F13 toF16, F17,  sCJD-VV2:F12, F14, F15 |
| **PPT1** | P50897 | Palmitoyl-protein thioesterase 1 | Ly | Novel | Ceroid lipofuscinosis, neuronal, 1 [43] | sCJD-MM1:F13 toF16, sCJD-MM2:F12 toF15,  sCJD-VV2:F12 |
| **SYN1** | P17600 | Synapsin-1 | Cj, Sy. Ga | Known [39] | Epilepsy X-linked, with variable learning disabilities and behavior disorders [38] | sCJD-MM1:F12, F16, F17,  sCJD-MM2:F13, F14, F16, F17,  sCJD-VV2:F14 to F17 |
| **SYN2** | Q92777 | Synapsin-2 | Cj, Sy. | Novel | Schizophrenia [38] | sCJD-MM1:F16, F17  sCJD-MM2:F14, F16, F17  sCJD-VV2:F15 toF17 |
| **PACN1** | Q9BY11 | Protein kinase C and casein kinase substrate in neurons protein 1 | Cy, Cp, Cj, Sy, Syo, Cp, | Novel |  | sCJD-MM1:F17  sCJD-MM2:F16, F17,  sCJD-VV2:F15, F17 |
| **COF1** | P23528 | Cofilin-1 | Nu, Cy, Ck, Cp | Known [7] | Creutzfeldt-Jakob-disease [18] | sCJD-MM1:F16, F17  sCJD-MM2:F12, F16, F17,  sCJD-VV2:F16, F17 |
| **CRYM** | Q14894 | Ketimine reductase mu-crystallin | Cy | Novel | Autosomal dominant, 40 deafness [19] | sCJD-MM1:F17,  sCJD-MM2:F16, F17,  sCJD-VV2:F16, F17 |
| **NSF** | P46459 | Vesicle-fusing ATPase | Cy | Novel |  | sCJD-MM1:F17,  sCJD-MM2:F16, F17,  sCJD-VV2:F16, F17 |
| **COF2** | Q9Y281 | Cofilin-2 | Nu matrix cy, Ck | Novel |  | sCJD-MM1:F16, F17,  sCJD-MM2:F12, F16, F17,  sCJD-VV2:F15, F17 |
| **IDH3A** | P50213 | Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial | Mc | Novel | Alzheimer’s disease [29] | sCJD-MM1:F17  sCJD-MM2:F12, F16, F17  sCJD-VV2:F16, F17 |
| **PROF2** | P35080 | Profilin-2 | Cy, Ck. | Novel | Creutzfeldt-Jakob-disease [30] | sCJD-MM1:F17,  sCJD-MM2:F17,  sCJD-VV2:F16, F17 |
| **NFL** | P07196 | Neurofilament light polypeptide (NF-L) |  | Novel | Prion diseases [33], familial Alzheimer’s disease [34] | sCJD-MM1:F17  sCJD-MM2:F17,  sCJD-VV2:F16, 17 |
| **KCC2G** | Q13555 | Calcium/calmodulin-dependent protein kinase type II subunit gamma | Sr membrane | Novel | Alzheimer’s disease [29] | sCJD-MM1:F13, F17  sCJD-MM2:F16, F17  sCJD-VV2:F16 |
| **GRP75** | P38646 | Stress-70 protein, mitochondrial | Mc, Nu, nucleolus | Novel |  | sCJD-MM1:F17,  sCJD-MM2:F12, F17  sCJD-VV2:F16 |
| **TPPP** | O94811 | Tubulin polymerization-promoting protein | Cy, Ck. Nu. Localizes to glial Lewy bodies | Novel | Known [38] | sCJD-MM1:F17,  sCJD-MM2:F17,  sCJD-VV2:F16 |

F12 to F17: HDF pool-12 to 17. Ce: centrosome, Sy: Synapse, Sr: sarcoplasmic reticulum, C: Cytoplasm, Ck: cytoskeleton, Nu: Nucleus, S: Secreted, Cm: Cell membrane, Sl: Sarcolemma, Ly: Lysosomes, Mc: Mitochondrion, Syo: Synaptosome, Cj: Cell junction, C V: cytoplasmic vesicles, Ga: Golgi apparatus, Pm: phagosome membrane, Px: peroxisome, Em: Endosome membrane, Cp: Cell projection, Gc: growth cone, Ms: Melanosome, Er: Endoplasmic reticulum and La: Lipid-anchor. The localization of proteins and accession number are assigned as in ExPASy protein database and Uniprot data base respectively. Relevance with AD, prion and PrP ligand were established by Uniprot database search as well.

Likewise, eleven proteins were uniquely identified in two sCJD subtype (i.e., MV and VV2)-specific HDFs. Respective reported PrP interaction, disease involvement and specific occurrence in subtype specific HDFs are enlisted in Suppl. table 4.

Suppl. table 4: High-density PrP (HDP) interactors commonly detected between the high-density fractions of sCJD-MM2 and sCJD-VV2 subtypes.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No.** | **Gene IDs** | **Entry** | **Protein names** | **Subcellular location** | **PrP-interaction** | **Involvement in disease** | **Occurrence in sub-type specific fractions** |
| 1 | DEST | P60981 | Destrin (Actin-depolymerizing factor) |  | Novel |  | sCJD-MM2:F12,  sCJD-VV2:F17 |
| 2 | COR1A | P31146 | Coronin-1A | C, Ck, C, C V, Pm | Novel |  | sCJD-MM2:F12,  sCJD-VV2:F16, F17 |
| 3 | SEPT3 | Q9UH03 | Neuronal-specific septin-3 | C, Ck, Cj, Sy | Novel |  | sCJD-MM2:F16, 17,  sCJD-VV2:F16, F17 |
| 4 | CISY | O75390 | Citrate synthase, mitochondrial | Mc | Novel |  | sCJD-MM2:F12. 17,  sCJD-VV2:F16, 17 |
| 5 | STX1B | P61266 | Syntaxin-1B | Nu, C, Ck, Ce | Novel | Generalized epilepsy with febrile seizures plus 9 [38] | sCJD-MM2:F17,  sCJD-VV2:F16, 17 |
| 6 | PRIO | P04156 | Major prion protein (PrP) | Cm; Ga, Nu | Known [35] | Transmissible spongiform encephalopathies (Kuru, CJD, FFI and GSS), Alzheimer's disease [36] | sCJD-MM2:F17,  sCJD-VV2:F15 to F17 |
| 7 | CNRP1 | Q96F85 | CB1 cannabinoid receptor-interacting protein 1 |  | Novel |  | sCJD-MM2:F17,  sCJD-VV2:F17 |
| 8 | SCRN1 | Q12765 | Secernin-1 | C | Novel |  | sCJD-MM2:F17,  sCJD-VV2:F16, 17 |
| 9 | UBA1 | P22314 | Ubiquitin-like modifier-activating enzyme 1 | C, Mc, Nu | Novel |  | sCJD-MM2:F17,  sCJD-VV2:F16, 17 |
| 10 | AINX | Q16352 | Alpha-internexin |  | Novel |  | sCJD-MM2:F17,  sCJD-VV2:F16, 17 |
| 11 | PRDX5 | P30044 | Peroxiredoxin-5, mitochondrial | Mc, C, Px | Novel |  | sCJD-MM2:F17,  sCJD-VV2:F16 |

F12 to F17: HDF pool-12 to 17. Ce: centrosome, Sy: Synapse, Sr: sarcoplasmic reticulum, C: Cytoplasm, Ck: cytoskeleton, Nu: Nucleus, S: Secreted, Cm: Cell membrane, Sl: Sarcolemma, Ly: Lysosomes, Mc: Mitochondrion, Syo: Synaptosome, Cj: Cell junction, C V: cytoplasmic vesicles, Ga: Golgi apparatus, Pm: phagosome membrane, Px: peroxisome, Em: Endosome membrane, Cp: Cell projection, Gc: growth cone, Ms: Melanosome, Er: Endoplasmic reticulum and La: Lipid-anchor. The localization of proteins and accession number are assigned as in ExPASy protein database and Uniprot database respectively. Relevance with AD, prion and PrP ligand were established by Uniprot database search as well.

Certain HDP-interactors were unique to certain subtype-specific high-density fractions from each disease subtype cohort. The disease relevance and reported interaction to PrP are detailed in the **additional file 7**. We could also identify three interactors common to the controls and spAD HDFs including cathepsin D (CTSD), catenin beta-1 (CTNNB1) and protein piccolo (PCLO).

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