Common neurodegeneration-associated proteins are physiologically expressed by antigen-presenting cells and are interconnected via the inflammation/autophagy-related proteins TRAF6 and SQSTM1

Serge Nataf*[1, 2, 3], Marine Guillen[2] and Laurent Pays[1, 2, 3]

[1]CarMeN Laboratory, INSERM U1060, INRA U1397, INSA de Lyon, Lyon-Sud Faculty of Medicine, University of Lyon, Pierre-Bénite, France.
[2]University of Lyon 1, Lyon, France.
[3]Banque de Tissus et de Cellules des Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France.

* Corresponding author: serge.nataf@inserm.fr

ABSTRACT

There is circumstantial evidence that, under neurodegenerative conditions, peptides deriving from aggregated or misfolded specific proteins elicit adaptive immune responses. On another hand, several genes involved in familial forms of neurodegenerative diseases were found to exert key innate immune functions. However, whether or not such observations are causally linked remains unknown. To start addressing this issue, we followed a systems biology strategy based on the mining of large proteomics and immunopeptidomics databases. First, we retrieved the expression patterns of common neurodegeneration-associated proteins in two professional antigen-presenting cells, namely B-cells and dendritic cells. Surprisingly, we found that under physiological conditions, numerous neurodegeneration-associated proteins are abundantly expressed by human B-cells. A survey of the human proteome allowed us to map a unique protein-protein interaction network linking common neurodegeneration-associated proteins and their first shell interactors in human B-cells. Surprisingly, network connectivity analysis identified two major hubs that both relate with inflammation and autophagy, namely TRAF6 (TNF Receptor Associated Factor 6) and SQSTM1 (Sequestosome-1). Moreover, the mapped network in B-cells also comprised two other hub proteins involved in both inflammation and autoimmunity: HSPA8 (Heat Shock Protein Family A Member 8 also known as HSC70) and HSP90AA1 (Heat Shock Protein 90 Alpha Family Class A Member 1). Based on these results, we then explored the Immune Epitope Database "IEDB-AR" and actually found that a large share of neurodegeneration-associated proteins were previously reported to provide endogenous MHC class II-binding peptides in human B-cells. Of note, peptides deriving from amyloid beta A4 protein, sequestosome-1 or profilin-1 were reported to bind multiple allele-specific MHC class II molecules. In contrast, peptides deriving from microtubule-associated

39 protein tau, presenilin 2 and serine/threonine-protein kinase TBK1 were exclusively reported
40 to bind MHC molecules encoded by the HLA-DRB1 1501 allele, a recently-identified
41 susceptibility gene for late onset Alzheimer's disease. Finally, we observed that the whole list
42 of proteins reported to provide endogenous MHC class II-binding peptides in human B-cells
43 is specifically enriched in neurodegeneration-associated proteins. Overall, our work indicates
44 that immunization against neurodegeneration-associated proteins might be a physiological
45 process which is shaped, at least in part, by B-cells.
46

47 **INTRODUCTION**

48 Multiple studies have now established that neurodegenerative disorders are not cell-
49 autonomous. The pathophysiological processes leading to neurodegeneration involve and
50 target not only neurons but also glial cells, including astrocytes, microglia and
51 oligodendrocytes (1–3). Moreover, beyond central nervous system (CNS) cells, the adaptive
52 immune system has emerged as a potentially important player. When considering only T-cell
53 responses, T-cell reactivity against amyloid beta peptides was already reported more than a
54 decade ago in both patients suffering from Alzheimer's disease (AD) and aged healthy
55 subjects (4). Recent works further demonstrated that alpha-synuclein (SNCA)-derived
56 peptides elicit helper and cytotoxic T-cell responses in a subgroup of Parkinson's disease (PD)
57 patients harboring specific major histocompatibility complex (MHC) alleles (5,6). Similarly, in
58 animal models of neurodegenerative disorders, T-cell responses against peptides deriving
59 from neurodegeneration-associated proteins were also demonstrated. In particular, in the
60 MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of PD, pathogenic brain-
61 infiltrating T-cells directed against SNCA were found to target the substantia nigra of
62 diseased mice (7,8). Along this line, in a mouse model of tauopathy, CD8 cytotoxic T-cells
63 directed against tau protein were shown to infiltrate the hippocampus and to drive cognitive
64 alterations (9). Finally, besides AD and PD, several studies provided evidence that T-cells are
65 activated during the course of Huntington's disease (HD), amyotrophic lateral sclerosis (ALS)
66 and/or their animal models (10–13). Nevertheless, the putative autoantigens targeted under
67 those conditions remain unknown.

68 Extending the functional results mentioned above, genome-wide association studies
69 (GWAS) have unraveled the central position of autoimmunity-related genes in the genetic
70 susceptibility landscape of neurodegenerative diseases (14–19). This is notably the case for

71 *HLA-DRB1* alleles which were recently demonstrated to confer increased risks of developing
72 PD (15) or late-onset AD (14). Also, two genes involved in familial forms of PD, namely *PINK1*
73 (PTEN-induced putative kinase 1) and *PRKN* (Parkin RBR E3 Ubiquitin Protein Ligase also
74 named PARK2 or Parkin) were shown to regulate the presentation of mitochondria-derived
75 antigens in the context of MHC class I molecules (20). Finally, innate immune functions were
76 demonstrated for several genes causatively-linked to familial forms of PD or ALS. These
77 comprise *C9ORF72* (21–23), *LRRK2* (Leucine-rich repeat kinase 2) (24–27), *GRN* (Granulin
78 Precursor) (28,29) as well as *PRKN* and *PINK1* (30–34).

79 However, advocating for the role of autoimmunity in neurodegenerative disorders
80 requires yet addressing several important issues. In particular, it appears crucial to
81 determine how T-cells directed against neurodegeneration-associated antigens are primed
82 in the periphery. The extent to which autoimmunity against neurodegeneration-associated
83 antigens might be a physiological event needs also to be assessed. Last but not least, a global
84 view on the expression of neurodegeneration-associated proteins by professional antigen-
85 presenting cells (APCs) is still lacking. In an attempt to address these issues, we used here a
86 systems biology approach embracing a large range of previously-published experimental
87 data. We notably explored in normal human APCs the expression patterns and reported
88 protein-protein interactions of the most common neurodegeneration-associated proteins.
89 Overall, our results indicate that in human B-cells, a large majority of neurodegeneration-
90 associated proteins are expressed at the protein level and form a complex network centered
91 on the inflammation/autophagy-related molecules SQSTM1 (Sequestosome-1) and TRAF6
92 (TNF Receptor Associated Factor 6). Finally, the analysis of MHC class II immunopeptidome
93 databases provides evidence that neurodegeneration-associated proteins expressed by

94 human B-cells are a source of endogenous peptides which are presented in the context of

95 HLA class II molecules.

96

97 **MATERIALS AND METHODS**

98 ***Workflow***

99 A scheme summarizing the workflow followed in the present work is shown in Figure 1.

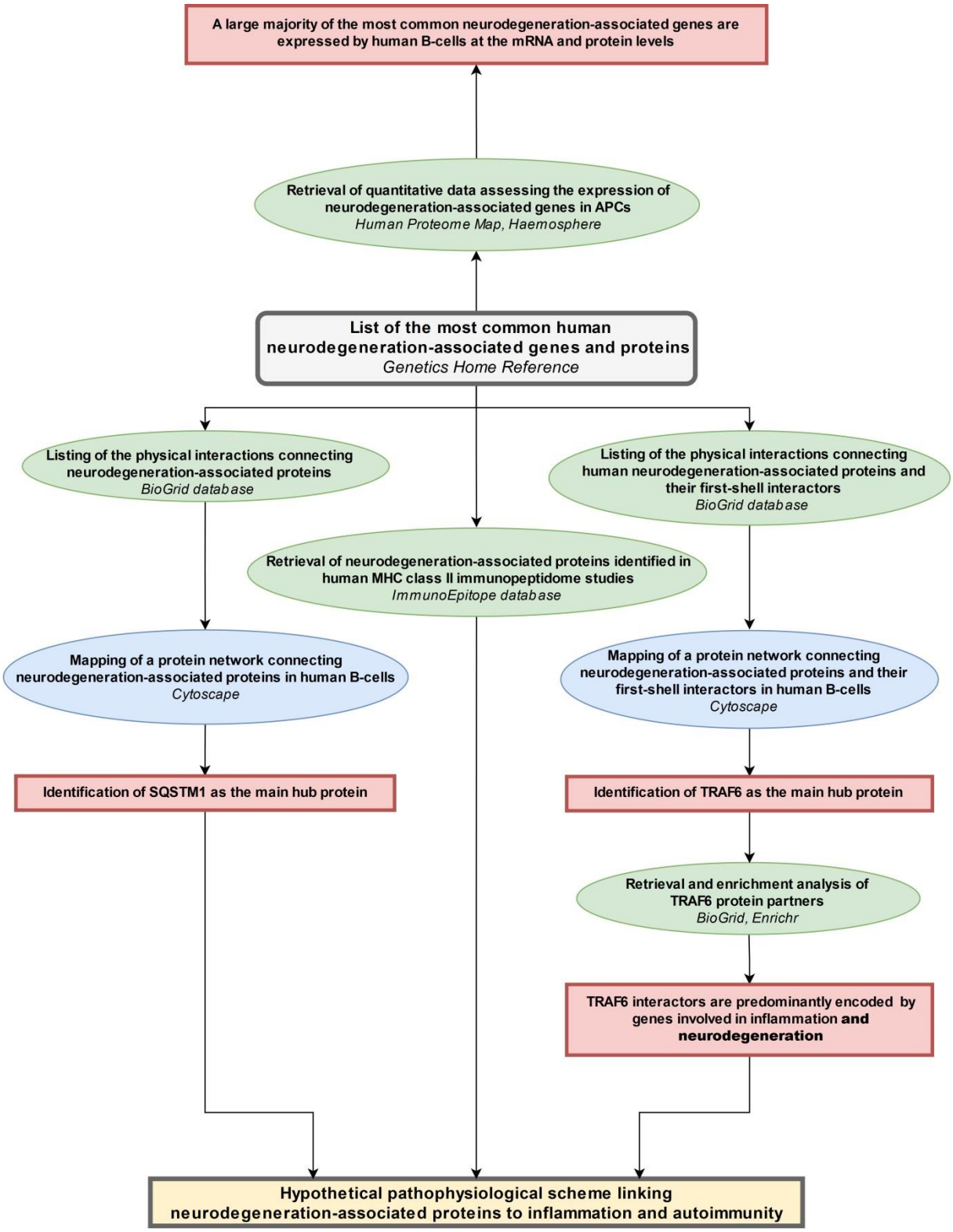


Figure 1: Workflow of the sudy. The workflow starts from the upper central grey rectangle. Other rectangles (yellow or red) frame the main results obtained following each of the analytical steps which are briefly described in ellipse shapes (green or blue). Terms in italics correspond to the name of the bioinformatics tools used for each analytical step. MHC: major histocompatibility complex; APCs: antigen-presenting cells.

107 ***Data mining methods and bioinformatics tools***

108 All the bioinformatics analyses were performed at least 3 times between March 2018 and
109 September 2019. Databases, bioinformatic tools and corresponding tasks performed in this
110 study are described below.

111 - The Genetics Home Reference website (35), is a regularly updated consumer health
112 resource from the National Library of Medicine. It provides information to the general public
113 about the effects of genetic variation on human health. In the present paper, we used the
114 "Genetics Home Reference" website to select without *a priori* the most common genetic
115 variations/alterations that are linked to the following neurodegenerative disorders:
116 Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease,
117 fronto-temporal dementia (FTD).

118 - The enrichment web platform Enrichr (36) perform enrichment analyses from queried lists
119 of genes. The Enrichr website allows surveying simultaneously 132 libraries gathering
120 245,575 terms and their associated lists of genes or proteins. Enrichment analysis tools
121 provided by the Enrichr bioinformatics platform provides adjusted P-values computed from
122 the Fisher's exact test. We focused our analysis on the "Jensen DISEASES" ontology library
123 (37) which is based exclusively on text-mining and allow determining whether a list of genes
124 is significantly associated with specific disease-related terms.

125 - The BioGrid database (38) compiles 29 169 experimentally-proven protein-protein
126 interactions connecting 23 098 human proteins. Querying the BioGrid database allows
127 retrieving for any given human protein the current list (update in 2019) of published
128 experimentally-identified human protein partners.

129 - The Human Proteome Map database (39) compiles protein expression data obtained by
130 mass spectrometry from human normal tissues and cells including a total of 85 human blood

131 samples from which the protein profiles of 6 blood-circulating cell types were established. In
132 parallel, we also explored 3 recently-published mass spectrometry datasets reporting on the
133 protemics profiles of blood-derived human B-cells (40), blood-derived human dendritic cells
134 (DCs) (41) and cultured monocyte-derived human dendritic cells (MoDCs)(42).

135 - The Immune Epitope Database and Analysis Resource (IEDB-AR) (43) compiles experimental
136 data on antibody and T-cell epitopes in humans, non-human primates and other animal
137 species. We followed a 3 step strategy as described below.

138 *Step 1: retrieval of a list of human MHC class II binding peptides and their parent*
139 *proteins*

140 - in the "Epitope" tab, the "Any Epitopes" item was marked
141 - in the "Assay" tab, the "MHC Ligand Assays" item was marked
142 - in the "Antigen" tab, "Homo sapiens" was entered in the "Organism" line
143 - in the "MHC restriction" tab, the "MHC class II" item was marked
144 - in the "Host" tab, the "Humans" item was marked
145 - in the "Disease" tab, the "Any Disease" item was marked.

146 Search was then launched and, from the results page, the "Assays" tab was selected
147 and a list of currently known ligands (peptides and parent proteins) of human MHC
148 molecules was retrieved.

149 *Step 2: filtering the results*

150 We retained only results which were both: i) obtained by mass spectrometry analysis
151 of peptides eluted from MHC class II molecules and ii) generated from cells of the B-
152 cell lineage, in the absence of immunization or stimulation protocols.

153 *Step 3: checking the reference IDs associated to each identified parent protein*

154 For each selected study and/or set of results, the reference ID associated to each
155 parent protein was checked on the UniProt website (44) in order to avoid
156 redundant or obsolete IDs.

157 - The Cytoscape software (45) is an open source software allowing to visualize complex
158 networks. We used the function "Network analysis" to identify hubs i.e objects exhibiting the
159 highest number of degrees (connections to other objects) in the generated networks.

160

161 ***Statistics***

162 When not embedded in bioinformatics webtools, statistics for enrichment analyses were
163 performed using the Fisher exact test. In particular, we assessed for several identified hub
164 proteins whether their retrieved list of partners (obtained via the BioGrid database) was
165 statistically enriched in neurodegeneration-associated proteins. To calculate enrichment
166 factors, we set the expected reference ratio as 0.002 which corresponds to the number of
167 common neurodegeneration-associated proteins (i.e 48 according to the "Home Genetics
168 Reference" website) over the number of coding genes for which interactors can be retrieved
169 from the BioGrid database (i.e 23098). The obtained p-values were then adjusted using
170 Bonferroni correction. The same approach was used to determine whether lists of parent
171 proteins from which derive human MHC class II-binding peptides are significantly enriched in
172 neurodegeneration-associated proteins.

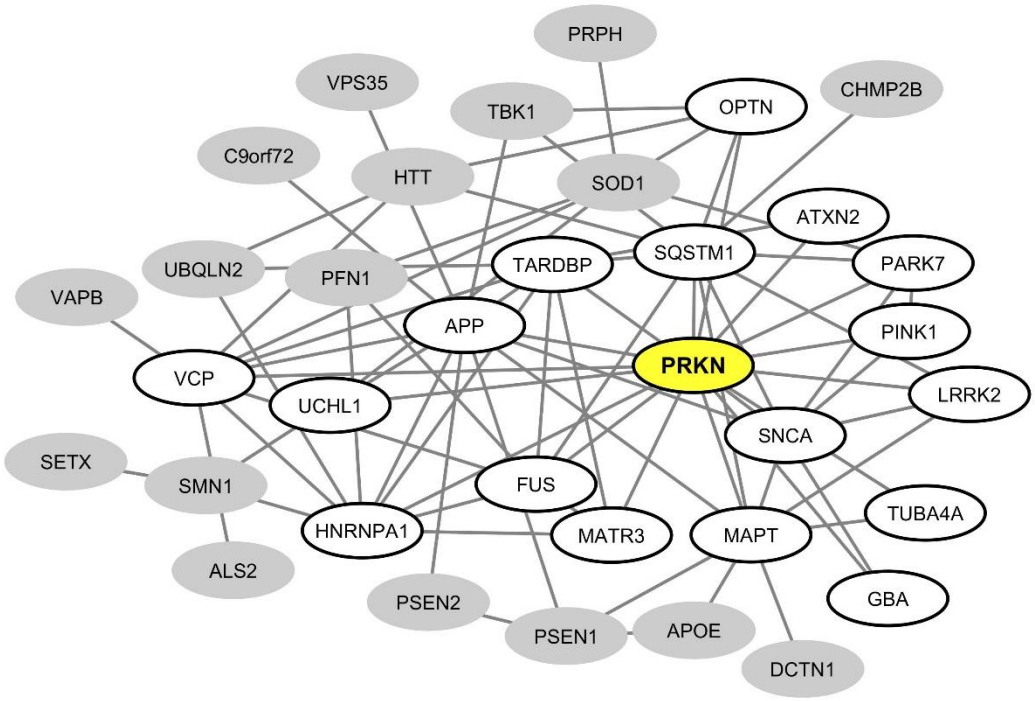
173

174 **RESULTS**

175

176 ***1- Neurodegeneration-associated proteins form a unique interaction network in which***
177 ***PRKN is the main hub***

178 From the most recently updated version of the human proteome compiled in the "BioGrid"
179 database, we extracted the currently published and experimentally-proven protein-protein
180 interactions connecting the most common neurodegeneration-associated proteins. Self-
181 interactions were excluded from our analysis. From these retrieved interactions we were
182 able to build and visualize a protein network which encompasses 35 (72%) of the 48 most
183 common neurodegeneration-associated proteins (Figure 2). Interestingly, network analysis
184 showed that PRKN harbored the highest number of interacting partners (n=17). Moreover,
185 when considering the whole list of known PRKN protein partners, the calculated enrichment
186 factor in neurodegeneration associated protein reached 18.97 and was highly significant
187 (Fisher exact test p-value: $3.35E^{-15}$). This result points to a yet unnoticed property of PRKN as
188 a major hub protein connecting a large array of proteins involved in not only PD but also ALS,
189 AD, Huntington's disease and/or FTD.



190

191 **Figure 2: Mapping of the protein-protein interaction network linking common**
192 **neurodegeneration-associated proteins irrespective of the cell type considered.** A survey of
193 the human proteome was performed by querying the protein-protein interaction database BioGRID

194 (38). Each node represents a protein indicated by the corresponding gene symbol and each edge
195 represents an experimentally-demonstrated protein-protein interaction. In this network, the "PRKN"
196 (Parkin) node, highlighted in yellow, exhibits the highest degree (i.e the highest number of direct
197 interactors). White nodes correspond to the first-shell partners of PRKN. Grey nodes are not direct
198 interactors of PRKN.
199

200 ***2- A majority of common neurodegeneration-associated proteins are abundantly***
201 ***expressed in human B-cells***

202 We then explored proteomics databases to determine whether neurodegeneration-
203 associated proteins are expressed by APCs under physiological conditions. Our search was
204 restricted to 2 cell lineages which harbor demonstrated antigen-presenting functions: B-cells
205 (46–48) and dendritic cells (DCs) (49–51). Results were combined with those retrieved from
206 proteomics data obtained in 3 independent studies by the mass spectrometry analysis of
207 human B-cells (40) or human dendritic cells (41,42) . Since mass spectrometry is a not a
208 sensitive technique, one may consider that detected proteins are abundantly expressed. As
209 shown in table 1, it is striking that 34 (70%) of 48 common neurodegeneration-associated
210 proteins are detectable by mass spectrometry in human B-cells (Table 1). In human DCs, 20
211 (41%) of 48 common neurodegeneration-associated proteins were detected and all of these
212 were also detected in human B-cells. Conversely, 14 common degeneration-associated
213 proteins were reported to be detected in B-cells but not DCs. These include notably
214 apolipoprotein E, amyloid beta A4 protein, presenilin-1 and alpha-synuclein.

215 **Table 1**

Gene Symbol	**Protein ID**	**Blood-derived B-cells** (39)	**Blood-derived B-cells** (40)	**Blood-derived DCs** (41)	**Cultured MoDCs** (42)
APOE	P02649	detected	detected	0	0
APP	P05067	detected	0	0	0
ATXN2	Q99700	detected	detected	0	0
CHMP2B	Q9UQN3	detected	detected	0	detected
DCTN1	Q14203	detected	detected	0	detected

FIG4	Q92562	detected	detected	0	0
FUS	P35637	detected	detected	detected	detected
GBA	P04062	0	detected	0	detected
GRN	P28799	detected	detected	0	0
HNRNPA1	P09651	detected	0	0	detected
HTT	P42858	detected	detected	detected	detected
LRRK2	Q5S007	detected	detected	detected	0
MATR3	P43243	detected	detected	detected	detected
OPTN	Q96CV9	detected	detected	0	0
PARK7	Q99497	detected	detected	detected	detected
PFN1	P07737	detected	detected	detected	detected
PRPH	P41219	detected	0	0	detected
PSEN1	P49768	detected	0	0	0
SETX	Q7Z333	detected	detected	0	detected
SIGMAR1	Q99720	detected	detected	0	0
SNCA	P37840	detected	0	0	0
SOD1	P00441	detected	detected	detected	detected
SPG11	Q96JI7	detected	detected	0	0
SQSTM1	Q13501	detected	detected	0	detected
TARDBP	Q13148	detected	0	detected	detected
TBK1	Q9UHD2	detected	detected	0	detected
TBP	P20226	detected	detected	0	0
TRPM7	Q96QT4	0	detected	0	0
TUBA4A	P68366	detected	0	0	detected
UBQLN2	Q9UHD9	detected	detected	0	0
UCHL1	P09936	detected	detected	0	0
VAPB	O95292	detected	detected	detected	detected
VCP	P55072	detected	detected	detected	detected
VPS35	Q96QK1	detected	detected	detected	detected

Table 1: Expression pattern of common neurodegeneration-associated proteins in human B-cells and human dendritic cells. The proteomics profiles of human circulating B-cells, circulating dendritic cells (DCs) or cultured monocyte-derived dendritic cells (MoDCs) were retrieved from 4 independent mass spectrometry studies (39–42). We found that 34 from 48 common neurodegeneration-associated proteins were detected by mass spectrometry in at least 1 of the explored studies. Interestingly, 14 common degeneration-associated proteins (highlighted in yellow) were reported to be detected in B-cells but not DCs. These include notably apolipoprotein E, amyloid beta A4 protein, presenilin-1 and alpha-synuclein. In contrast, when detected in DCs, common neurodegeneration-associated proteins were constantly detected in B-cells.

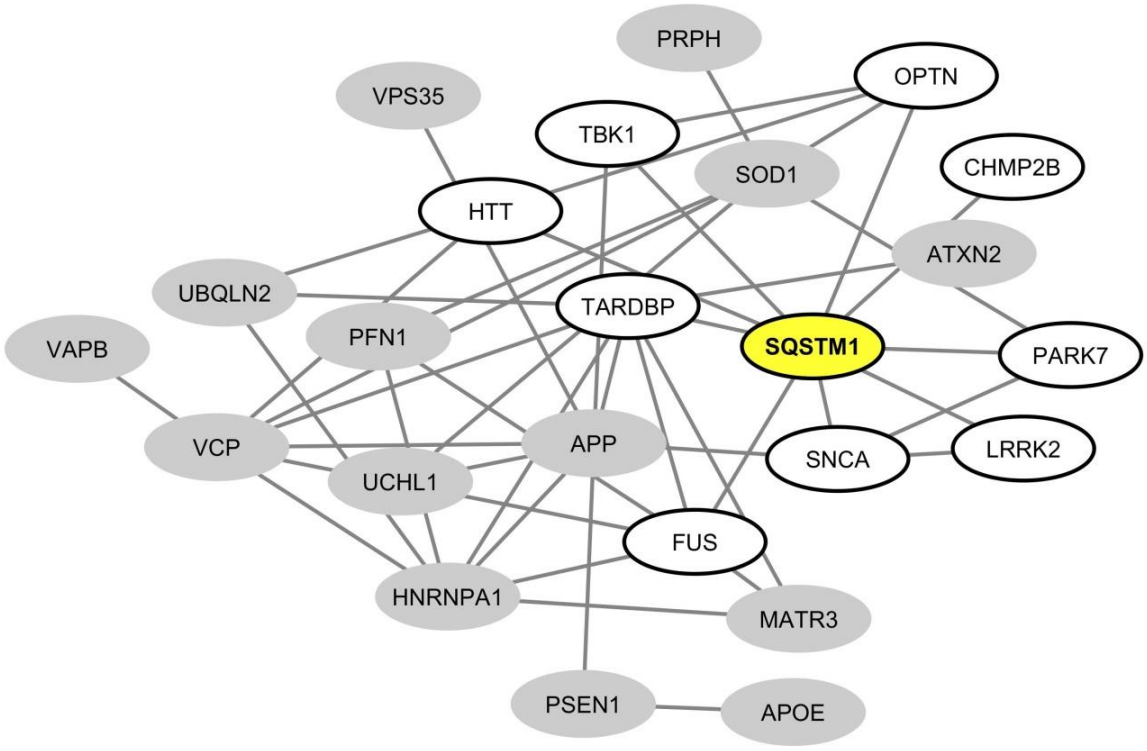
Of note, in both human B-cells and DCs, *PRKN* was not detected at the protein level by mass spectrometry. This finding urged us to identify the main hub protein(s) which may

229 interconnect abundantly-expressed neurodegeneration-associated proteins in human B-
230 cells.

231

232 ***3- Neurodegeneration-associated proteins expressed by human B-cells form a unique***
233 ***interaction network in which the inflammation/autophagy-related protein SQSTM1 is the***
234 ***main hub***

235 From the interaction network depicted in Figure 2 we only retained nodes corresponding to
236 neurodegeneration-associated genes that are detectable by mass spectrometry in human B-
237 cells. We observed that in this cell type, 24 neurodegeneration-associated proteins are
238 predicted to form a tight interaction network which is centered on the
239 inflammation/autophagy-related protein SQSTM1.



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241 **<u>Figure 5: Mapping of the protein-protein interaction network linking common</u>**
242 **<u>neurodegeneration-associated proteins in human B-cells.</u>** A survey of the human proteome

243 was performed by querying the protein-protein interaction database BioGRID (38). Each node
244 represents a protein indicated by the corresponding gene symbol and each edge represents an
245 experimentally-demonstrated protein-protein interaction. In this network, the "SQSTM1"
246 (Sequestosome-1) node, highlighted in yellow, exhibits the highest degree (i.e the highest number of
247 direct interactors). White nodes correspond to the first-shell partners of SQSTM1 in human B-cells.
248 Grey nodes are expressed by B-cells but are not direct interactors of SQSTM1.
249

250 ***4- The protein network formed by neurodegeneration-associated proteins connects with a***
251 ***set of first shell interactors among which the B-cell inflammation/autophagy-related***
252 ***protein TRAF6 is the main hub***

253 To extend these data, we then retrieved from the "BioGrid" database the currently known
254 and experimentally-demonstrated interactors of common neurodegeneration-associated
255 proteins, irrespective of their levels of expression in human B-cells. From this list, we
256 extracted candidate hub proteins interacting with more than 10 neurodegeneration-
257 associated proteins. For each of these candidate hubs, total lists of protein interactors were
258 then retrieved from BioGrid and a Fisher exact test was applied so to determine if
259 neurodegeneration-associated proteins were actually significantly enriched in each
260 established list. By this mean, we were able to assign an enrichment factor and an associated
261 p-value to each candidate hub. This approach allowed us to identify 20 hub proteins (Table
262 2) with which common neurodegeneration-associated proteins are specifically connected.
263 Among these 20 hub proteins, 10 are expressed at the protein level as assessed via the
264 "Human Proteome Map" database (39). Of note, from the 10 hub proteins exhibiting the
265 most significant and highest enrichment factors, 8 are abundantly expressed by human B-
266 cells. These include: i) the heat shock proteins HSPA8 (also named HSC70), HSPA4 (also
267 named HSP70) and HSP90AA1 (also named HSP90) which are all involved in both antigen
268 presentation by MHC class II molecules (52–54) and the modulation of T-cell responses (55–
269 57) and ii) YWHAZ and YWHAQ proteins also known as 14-3-3 protein zeta and theta

270 respectively, which bind MHC class II molecules (58,59) and are implicated in various
271 neurodegenerative diseases (60–62). Finally, unexpectedly, the most significant hub we
272 identified was TRAF6 (TNF receptor associated factor 6), an inflammation/autoimmunity-
273 related molecule (63,64) playing a major role in the control of B-cell activation (65,66).
274 Indeed, the whole list of TRAF6 interactors comprises 17 neurodegeneration-associated
275 proteins which corresponds to an enrichment factor of 27.68 and an adjusted p-value of
276 $1.57E^{-16}$.

277 **Table 2**

Gene symbol	Protein ID	Protein partners	ND-associated protein partners	Enrichment factor	Adjusted p-value
TRAF6	Q9Y4K3	307	17	27.68	1.37E-16
PRKN	O60260	448	17	18.97	6.71E-14
HSPA4	P34932	363	13	17.90	1.58E-10
SQSTM1	Q13501	294	12	20.40	2.03E-10
HSPA8	P11142	708	16	11.29	8.20E-10
YWHAZ	P63104	412	12	14.56	9.38E-9
HSP90AA1	P07900	839	15	8.93	6.65E-08
YWHAQ	P27348	476	11	11.55	4.74E-07
CYLD	Q9NQC7	620	12	9.67	8.15E-07
CTNNB1	P35222	616	11	8.92	6.00E-06
UBC	P0CG48	1050	14	6.66	6.54E-06
TP53	P04637	1062	14	6.59	7.46E-06
CUL7	Q14999	658	11	8.35	1.13E-05
EGFR	P00533	1224	14	5.71	3.73E-05
RNF4	P78317	1251	14	5.59	4.75E-05
MCM2	P49736	940	11	5.85	3.09E-04
BRCA1	P38398	962	11	5.71	3.80E-04
NTRK1	P04629	1948	16	4.10	4.54E-04
CUL3	Q13618	1227	13	5.29	1.75E-04
ESR2	Q92731	2249	13	2.89	4.67E-02

278 **Legend:** A survey of the human proteome was performed by querying the protein-protein interaction
279 database BioGRID (38). Candidate hub proteins interacting with more than 10 common
280 neurodegeneration-associated proteins were retrieved. The lists of partners currently demonstrated
281 for each of these candidate hubs were then retrieved. For each of these lists, a factor of enrichment
282 in neurodegeneration-associated proteins was established along with an associated Fisher's exact
283 test p-value, as described in the Materials and Methods section. From left to right, gene symbols and
284 corresponding protein IDs of the identified hub proteins are shown in the first and second column,
285 the associated total numbers of partners and total numbers of neurodegeneration (ND)-associated

286 protein interactors are shown in the third and fourth column. The corresponding enrichment factors
287 and adjusted p-values are shown in the last two columns. Proteins that are detectable by mass
288 spectrometry in human B-cells, according to the "Human Proteome Map" database (39), are
289 highlighted in yellow.
290

291 However, one may argue that the list of currently-known TRAF6 partners might be enriched
292 in not only neurodegeneration-associated proteins but also many other sets of proteins
293 which do not relate with neurodegeneration. To address this issue, we performed on the
294 whole list of TRAF6 partners a non *a priori* enrichment analysis using the "JENSEN Disease"
295 text-mining webtool (37) embedded in the "Enrichr" analysis platform (36). Results shown in
296 Table 3 indicate that the 10 disease-related terms with which TRAF6 partners are the most
297 significantly associated comprise the terms "Frontotemporal dementia",
298 "Neurodegenerative disease" and "Pick's disease". This finding points to a specific link
299 between TRAF6 and neurodegeneration.

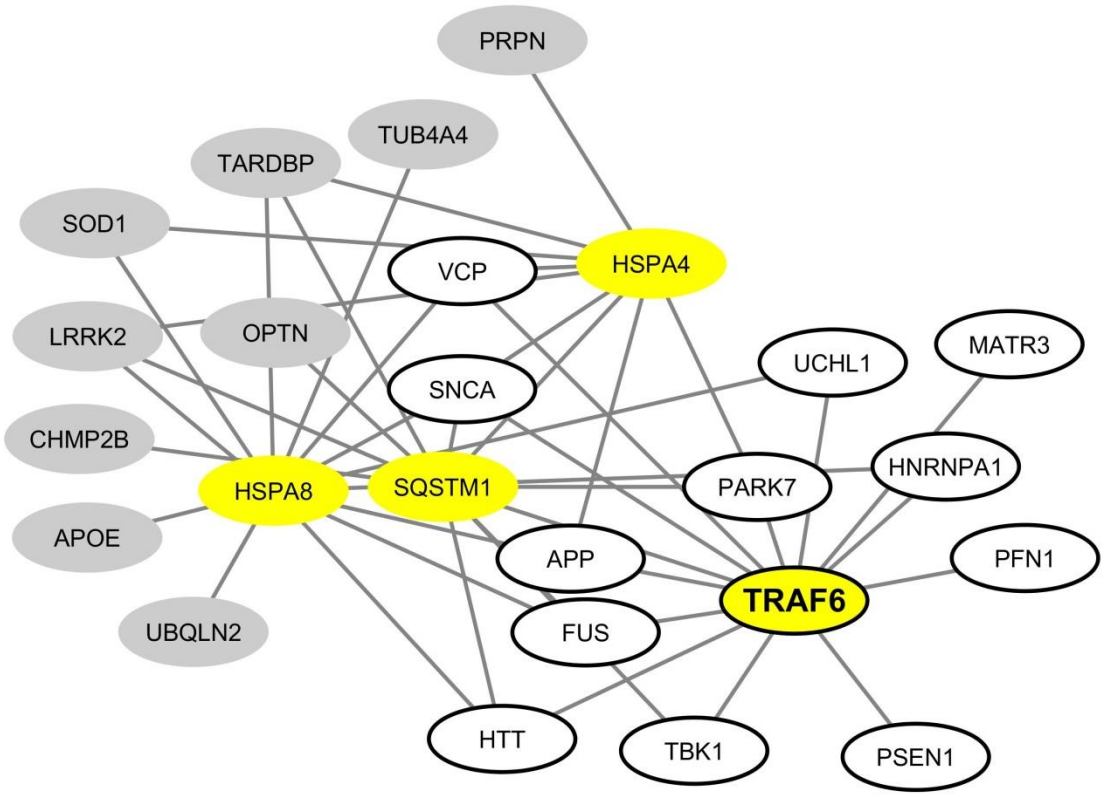
300 **Table 3**

Disease Enrichment	
Term	Adjusted p-value
Cancer	5.09E-7
Frontotemporal dementia	2.69E-6
Hypohidrotic ectodermal dysplasia	2.75E-6
Toxic encephalopathy	3.20E-6
Mulibrey nanism	3.21E-6
Neurodegenerative disease	3.45E-6
Arthritis	4.14E-6
Influenza	8.77E-6
Pick's disease	1.93E-4
Leishmaniasis	3.72E-4

301 **Legend:** A survey of the human proteome was performed by querying the protein-protein interaction
302 database BioGRID (38). The list of currently known and experimentally-demonstrated TRAF6 partners
303 was retrieved. From this list of interactors, an enrichment analysis with the "JENSEN Disease" text-
304 mining webtool (37) embedded in the "Enrichr" analysis platform (36) was then performed. Shown
305 are the disease-related terms exhibiting the 10 most statistically significant enrichments. Terms
306 relating with neurodegeneration are highlighted in yellow.
307

308 As a control and to further establish the specificity of our findings, we assessed whether
309 similar results would be obtained from a list of common demyelination-associated proteins
310 i.e. proteins commonly considered as candidate autoantigens in multiple sclerosis (67). We
311 found that neither TRAF6 nor the other hubs linking common neurodegeneration-associated
312 proteins exhibited lists of protein partners which were significantly enriched in common
313 demyelination-associated proteins (data supplement 1).

314 From these results we then built and visualized a B-cell protein-protein interaction
315 network encompassing the most significant hub proteins and their neurodegeneration-
316 associated interactors expressed in B-cells (Figure 5). We observed that from the 32
317 neurodegeneration-associated proteins expressed by B-cells, 22 (68%) are first shell
318 interactors of HSPA4, HSPA8, TRAF6 or SQSTM1. These results unravel a yet unknown
319 function of these molecules as major hub proteins connecting in B-cells a large array of
320 proteins involved in PD, ALS, AD, Huntington's disease and/or FTD.



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322

323 **Figure 6: Mapping of the protein-protein interaction network linking common**
324 **neurodegeneration-associated proteins and their hub protein partners in human B-cells.** A
325 survey of the human proteome was performed by querying the protein-protein interaction database
326 BioGRID (38). Only proteins expressed by human B-cells according to the "Human Proteome Map"
327 database (39) were taken into account. Each node represents a protein indicated by its
328 corresponding gene symbol. The 4 hub proteins expressed by B-cells and whose partners exhibited
329 the most significant and highest enrichment factors in neurodegeneration-associated proteins are
330 highlighted in yellow. The neurodegeneration-associated proteins expressed by B-cells and
331 interacting with TRAF6 are shown in white ellipses. Other neurodegeneration-associated proteins
332 involved in this network are shown in grey ellipses.
333

334 ***5- Common neurodegeneration-associated proteins provide a source of endogenous MHC***

335 ***class II-binding peptides in human B-cells***

336 While peptides presented by MHC class II molecules are classically generated by the
337 proteolysis of phagocytized exogenous antigens, the presentation of endogenous peptides
338 by MHC class II molecules is an alternate pathway which has been robustly documented (68–
339 71). We thus surveyed the Immune Epitope DataBase (IEDB-AR) (43) to assess whether
340 peptides derived from neurodegeneration-associated proteins had been previously
341 identified as binding MHC class II molecules in immunopeptidome studies which used human
342 cells of the B-cell lineage as a source of endogenous peptides. Of note, we excluded studies
343 assessing the MHC binding of exogenously-provided specific peptides and retained only
344 works relying on the systematic mass spectrometry-based identification of peptides eluted
345 from MHC class II molecules. In addition, we excluded experiments in which immunization or
346 stimulation protocols were applied to B-cells. On this basis, we retained 19 studies (data
347 supplement 2) which were performed on cells of the B-cell lineage including predominantly
348 Epstein-Barr virus (EBV)-transformed B-cells. When screening these studies, we found that
349 23 out of 48 common neurodegeneration-associated proteins were reported to provide
350 endogenous MHC class II-binding peptides in B-cells (Table 4 and data supplement 2). The

351 most frequently identified neurodegeneration-associated parent proteins are abundantly
352 expressed in B-cells and comprise notably the proteins encoded by: i) the AD-related genes
353 *APP* and *PSEN1*, ii) the ALS/FTD-related genes *PFN1*, *SQSTM1*, *GRN*, *SOD1* and *VCP* and iii)
354 the PD-related proteins *PARK7* and *GBA* (Figure 1).

355 **Table 4**

Neurodegeneration-associated proteins	Reported MHC class II restrictions
Amyloid beta A4 protein (*APP*)	HLA class II, HLA-DQ, HLA-DR, HLA-DR3, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2, HLA-DRB1*15:01 (HLA-DR15), HLA-DRB5*01:01 (HLA-DR51), HLA-DRB1*04:05 (HLA-DR4), HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5)
Sequestosome-1 (*SQSTM1*)	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2, HLA-DR15/DR51, HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5)
Profilin-1 (*PFN1*)	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DR3, HLA-DRB1*04:05 (HLA-DR4), HLA-DR15/DR51
Superoxide dismutase [Cu-Zn] (*SOD1*)	HLA class II, HLA-DR, HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2
Transitional endoplasmic reticulum ATPase (*VCP*)	HLA class II, HLA-DR, HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2
Lysosomal acid glucosylceramidase (*GBA)*	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DR15, HLA-DRB1*04:05 (HLA-DR4)
Presenilin-1 (*PSEN1*)	HLA class II, HLA-DQ, HLA-DQ2.2, HLA-DR15/DR51, HLA-DRB1*04:05 (HLA-DR4)
Ubiquilin-2 (*UBQLN2*)	HLA class II, HLA-DR1, HLA-DQ7.5,

	HLA-DQ2.2, HLA-DRB1*04:05 (HLA-DR4)
Major prion protein (*PRNP*)	HLA-DQ, HLA-DR, HLA-DR1, HLA-DQ7.5, HLA-DQ2.2
Vacuolar protein sorting-associated protein 35 (*VPS35*)	HLA class II, HLA-DR , HLA-DR15/DR51, HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5)
Optineurin (*OPTN*)	HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2
Protein deglycase DJ-1 (*PARK7*)	HLA class II, HLA-DR1, HLA-DRB1*04:01 (HLA-DR4), HLA-DRB1*04:05 (HLA-DR4)
Progranulin (*GRN*)	HLA class II, HLA-DQ, HLA-DQ7.5
Spatacsin (*SPG11*)	HLA-DQ7.5, HLA-DQ2.2
Ubiquitin carboxyl-terminal hydrolase isozyme L1 (*UCHL1*)	HLA class II, HLA-DR
RNA-binding protein FUS (*FUS*)	HLA class II
Probable cation-transporting ATPase 13A2 (*ATP13A2*)	HLA-DR
Heterogeneous nuclear ribonucleoprotein A1 (*HNRNPA1*)	HLA class II
Charged multivesicular body protein 2b (*CHMP2B*)	HLA-DQ7.5
Huntingtin (*HTT*)	HLA-DR
Serine/threonine-protein kinase TBK1 (*TBK1*)	HLA-DR15/DR51
Presenilin-2 (*PSEN2*)	HLA-DR15/DR51
Microtubule-associated protein tau (*MAPT*)	HLA-DR15/DR51

Legend: The "IEDB-AR" immune epitope database (43) was screened in order to retain only publications reporting on the systematic mass spectrometry identification of endogenous peptides binding MHC-class II molecules in the human B-cell lineage. Only results obtained on human cells of the B-cell lineage in the absence of immunization or stimulation protocols were taken into account. The retrieved list of parent proteins and corresponding reported MHC class II restriction of derived peptides was then crossed with the list of 48 common neurodegeneration-associated proteins we established. The protein names and gene symbols are shown in the left column; the corresponding reported MHC class II restrictions of derived peptides are shown in the right column. When needed, aliases frequently used in the HLA class II genotype/serotype nomenclature are indicated in brackets.

6- Hub molecules linking common neurodegeneration-associated proteins provide a source of endogenous MHC class II-binding peptides in human B-cells

From the 19 relevant B-cell studies we retained on IEDB-AR, we also attempted to determine whether the hub molecules we identified as linking neurodegeneration-associated proteins in B-cells (Table 2) were, in parallel, reported to provide endogenous ligands for MHC class II molecules in B-cells. We found that from 10 candidate hubs abundantly expressed by B-cells,

372 8 were reported to provide endogenous ligands for MHC class II molecules in human B-cells

373 (Table 5 and data supplement 2).

374

375 **Table 5**

Hub molecules linking common neurodegeneration-associated proteins	Reported MHC class II restriction
Heat shock cognate 71 kDa protein (*HSPA8*)	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2, HLA-DR3, HLA-DRB1*15:01 (HLA-DR15), HLA-DR15/DR51, HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5), HLA-DRB1*04:01 (HLA-DR4), HLA-DRB1*04:05 (HLA-DR4)
Sequestosome-1 (*SQSTM1*)	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2, HLA-DR15/DR51, HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5)
Heat shock protein HSP 90-alpha (*HSP90AA1*)	HLA class II, HLA-DR, HLA-DQ, HLA-DQ7.5, HLA-DQ2.5, HLA-DQ2.2, HLA-DRB1*04:05 (HLA-DR4), HLA-DRB1*15:01 (HLA-DR15) HLA-DQA1*05:01/DQB1*02:01 (HLA-DQ2.5)
14-3-3 protein zeta/delta (*YWHAZ*)	HLA class II, HLA-DR, HLA-DQ, HLA-DR1, HLA-DRB1*04:05 (HLA-DR4)
14-3-3 protein theta (*YWHAQ*)	HLA class II, HLA-DQ, HLA-DRB1*04:05 (HLA-DR4)
Heat shock 70 kDa protein 4 (*HSPA4*)	HLA-DR, HLA-DR3
Ubiquitin carboxyl-terminal hydrolase CYLD (*CYLD*)	HLA-DRB1*04:05 (HLA-DR4)
TNF receptor-associated factor 6 (*TRAF6*)	HLA-DR1

376 **Legend:** The "IEDB-AR" immune epitope database (43) was screened in order to retain only
377 publications reporting on the systematic mass spectrometry identification of endogenous peptides
378 binding MHC-class II molecules in the human B-cell lineage. Only results obtained in the absence of
379 immunization or stimulation protocols were taken into account. The retrieved list of parent proteins
380 and corresponding reported MHC class II restriction of derived peptides was then crossed with the
381 list of 11 hub molecules being abundantly expressed by human B-cells and linking common
382 neurodegeneration-associated. The protein names and corresponding gene symbols are shown in the
383 left column; the corresponding reported MHC class II restrictions of derived peptides are shown in

384 the right column. When needed, aliases frequently used in the HLA class II genotype/serotype
385 nomenclature are indicated in brackets.
386

387 Among these 8 hubs, HSPA8 was the parent protein being the most frequently identified as
388 providing endogenous peptides which bind MHC class II molecules in human B-cells (Table
389 5).

390

391 ***7- In human B-cells, the list of parent proteins from which derive endogenous MHC class II-***
392 ***binding peptides is specifically enriched in neurodegeneration-associated proteins***

393 The whole list of parent proteins identified as providing MHC class II-binding endogenous
394 peptides in B-cells was retrieved from IEDB-AR and an enrichment analysis was performed to
395 determine whether such a list was significantly enriched in neurodegeneration-associated
396 proteins. We found that genes coding for neurodegeneration-associated proteins
397 encompassed 0.62% (22 out of 3523) of the whole genes coding for such parent proteins
398 (data supplement 3), which corresponds to an enrichment of 2.58 (p-value = 0.0006, Fisher
399 exact test) when considering the whole number of human protein-coding genes as roughly
400 20 000 (72). To confirm these results and assess their level of specificity, we used the
401 "JENSEN Disease" text-mining webtool (37) and performed an unsupervised enrichment
402 analysis from the whole list of genes coding for parent proteins previously identified as
403 providing MHC class II-binding peptides in human B-cells (data supplement 3). From this list
404 of 3522 genes, 96 (2.72%) were annotated with the term "Neurodegenerative disease" (data
405 supplement 3) which corresponds to the second most significant enrichment, after the term
406 "Arthritis" (Table 6).

407

408 **Table 6**

Disease Enrichment	
Term	Adjusted p-value
Arthritis	3.94E-8
Neurodegenerative disease	1.80E-7
Lupus erythematosus	4.92E-7
Tetanus	2.07E-5
Human immunodeficiency virus infectious disease	4.80E-5
Diamond-Blackfan anemia	7.10E-5
Coronary artery disease	1.57E-4
Fabry disease	2.08E-4
Inclusion-cell disease	2.16E-4
Neuropathy	1.97E-4

409 **Legend:** The "IEDB-AR" immune epitope database (43) was screened in order to retain only
410 publications reporting on the systematic mass spectrometry identification of endogenous peptides
411 binding MHC class II molecules in the human B-cell lineage. Only results obtained in the absence of
412 immunization or stimulation protocols were taken into account. The parent proteins from which
413 derive the identified bound peptides were retrieved and the list of corresponding coding genes was
414 submitted to an enrichment analysis with the "JENSEN Disease" text-mining webtool (37) embedded
415 in the "Enrichr" analysis platform (36). The 10 most significant terms associated with this list of genes
416 are shown. The second most significant enrichment is observed for the term "Neurodegenerative
417 disease" (term and corresponding adjusted p-value highlighted in yellow).
418
419

420 Since the HLA-DRB1 1501 allele (corresponding to the HLA-DR15 serotype) was recently
421 identified as a risk factor for sporadic forms of late onset AD (14), we retrieved the whole list
422 of parent proteins (and corresponding coding genes) which, in human B-cells, were
423 previously reported to provide peptides that bind HLA-DRB1 1501-encoded MHC class II
424 molecules. Importantly, such a list was significantly enriched in neurodegeneration-
425 associated proteins (enrichment factor: 5.34; p-value = 0.0003, Fisher exact test). Moreover,
426 when this list of parent proteins was submitted to an unsupervised enrichment analysis, the
427 term "Neurodegenerative disease" was found to reach the highest level of statistical
428 significance (Table 7).

429 **Table 7**

Disease Enrichment	
Term	Adjusted p-value
Neurodegenerative disease	3.31E-6
Allergic hypersensitivity disease	1.70E-4
Influenza	1.34E-4
Inclusion-cell disease	1.64E-3
Diamond-Blackfan anemia	2.12E-3
Gangliosidosis	1.77E-3
Lysosomal storage disease	2.55E-3
Lupus erythematosus	2.41E-3
Dementia	2.57E-3
Collagen disease	2.62E-3

Legend: The "IEDB-AR" immune epitope database (43) was screened in order to retain only publications reporting on the systematic mass spectrometry identification of endogenous peptides which bind HLA-DRB1 1501-encoded MHC class II molecules in the human B-cell lineage. Only results obtained in the absence of immunization or stimulation protocols were taken into account. The parent proteins from which derive the identified bound peptides were retrieved and the list of corresponding coding genes was submitted to an enrichment analysis with the "JENSEN Disease" text-mining webtool (37) embedded in the "Enrichr" analysis platform (36). Shown are the disease-related terms exhibiting the 10 most statistically significant enrichments. Terms relating with neurodegeneration are highlighted in yellow.

Finally, based on the IEDB-AR survey we performed, HLA-DRB1 1501-encoded MHC class II molecules are the only HLA class II molecules which, in human B-cells, were reported to bind endogenous peptides deriving from microtubule-associated protein tau, presenilin-2 or serine/threonine-protein kinase TBK1 (Table 4 and data supplement 2).

445 **DISCUSSION**

446 In the present work, we mined large publically-available databases to provide
447 experiment-based evidence of a link between neurodegeneration and autoimmunity. Using
448 a systems biology approach we report that a large range of common neurodegeneration-
449 associated proteins: i) are expressed by human B-cells under physiological conditions, ii)
450 form a comprehensive and functionally-relevant protein-protein interaction network in
451 human B-cells and iii) provide endogenous peptides which bind MHC class-II molecules in
452 human B-cells. Patients suffering from neurodegenerative conditions exhibit T cell- and/or
453 antibody-mediated responses directed against major neurodegeneration-associated proteins
454 such as amyloid beta A4 protein, alpha-synuclein and tau protein (4–6,73). However,
455 naturally-occurring antibodies against amyloid-beta (74), alpha-synuclein (75–77) and tau
456 protein (73,77,78) were also demonstrated in cohorts of healthy subjects. Similarly, apart
457 from any pathological context, robust T-cell responses against peptides deriving from tau
458 protein were recently demonstrated to widely occur in the general population (79).These
459 findings suggest that the autoimmune processes described in patients with
460 neurodegenerative conditions might be shaped by pre-existing physiological autoimmune
461 responses directed against common neurodegeneration-associated proteins. It is worth
462 noting that, while physiological autoimmunity was firmly demonstrated nearly 50 years ago
463 (80–82), the intimate nature of the links bridging physiological autoimmunity to its
464 pathological counterpart is still matter of debate. Numerous functions have been assigned to
465 physiological autoimmunity (83,84), including, more recently, a support to cognition (85–90).
466 In line with these findings, our data indicate that a specific set of brain antigens expressed by
467 B-cells and involved in neurodegenerative diseases might prime a neuroprotective and,
468 possibly, cognition-promoting T-cell response under physiological conditions. Of note, B-cells

469 are now recognized as professional APCs and, as such, are able to prime naïve CD4 T-cells
470 with a similar efficiency than DCs (91,92). The autophagy of cytosolic and nuclear proteins in
471 B-cells was shown to provide a continuous source of endogenous MHC class-II ligands (93).
472 Moreover, such autophagosome-derived peptides induce the proliferation of autologous T-
473 cells under *in vitro* conditions (94). However, that neurodegeneration-associated proteins
474 provide MHC class II-binding endogenous peptides in B-cells neither prove that T-cells are
475 actually primed against such peptides *in vivo* nor that peptide deriving from misfolded
476 neurodegeneration-associated proteins are presented by B-cells under neurodegenerative
477 conditions. Moreover, even if it was actually the case, the phenotype of autoreactive T-cells
478 generated via such a mechanism would need to be explored. More generally, one has to
479 keep in mind that no consensus has been currently reached regarding the phenotype of
480 physiological autoreactive T-cells. Thus, both autoreactive Tregs and autoreactive pro-
481 inflammatory T-cells belong to the physiological T-cell repertoire and were both found to
482 exert neuroprotective effects (95–98). Finally, the picture might be even more tangling since
483 Tregs were demonstrated to prevent autoimmunity by restraining autophagy in APCs (99).

484 Several genes involved in familial forms of neurodegenerative disorders exert key
485 functions in the autophagy pathway. These notably comprise PRKN, PINK1 and SQSTM1
486 (100–103). In the recent years, major works provided evidence that, in neurons and immune
487 cells, functional defects in such genes hamper mitophagy (a specialized form of autophagy),
488 stimulate the inflammasome pathway and foster the presentation of mitochondrial antigens
489 by MHC class I molecules (33,104,105). However, these findings do not render account for
490 the existence of HLA class II-restricted T-cell responses against neurodegeneration-
491 associated proteins. Moreover, antigens targeted by autoimmunity during
492 neurodegenerative conditions are far from deriving only from the mitochondrial

493 compartment. In this regard, our work suggests that in B-cells, the inflammation/autophagy-
494 related molecules SQSTM1 and TRAF6 are crucially involved in the presentation of
495 neurodegeneration-associated antigens by MHC class II molecules.

496 The mining of previously published mass spectrometry analyses performed on MHC
497 class II-eluted peptides showed that, in human B-cells, several neurodegeneration-
498 associated proteins provide endogenous peptides which bind a large range of MHC class II
499 alleles. This is notably the case for amyloid beta A4 protein, sequestosome-1 and profilin-1.
500 Similarly, peptides deriving from HSPA8, a hub molecule which links a high number of
501 neurodegeneration-associated proteins, bind multiple MHC class II alleles. Our observations
502 suggest that these 4 molecules are likely to elicit immune responses in a large range of the
503 human population. Determining whether or not such antigens are targeted by cognition-
504 promoting autoimmunity is a potentially important issue. On another hand, in human B-
505 cells, several neurodegeneration-associated antigens appear to provide endogenous
506 peptides harboring an allele-specific MHC class II restriction in B-cells. For e.g. endogenous
507 peptides deriving from microtubule-associated protein tau, PSEN2 and Serine/threonine-
508 protein kinase TBK1 were exclusively reported to bind HLA-DRB1 1501-encoded MHC class II
509 molecules under the experimental conditions described above. Since the HLA-DRB1 1501
510 allele is a susceptibility gene for late onset AD (14), this may prove to be of interest in the
511 context of AD pathophysiology. However, additional studies are clearly needed in order to
512 establish, under strictly comparable conditions, the endogenous immunopeptidomes of
513 distinct MHC class II alleles in B-cells. Moreover, it should be reminded that the endogenous
514 immunopeptidome of MHC class II molecules does not match the corresponding repertoire
515 of exogenous peptides (106). Since a widespread T-cell reactivity against Tau peptides was
516 recently demonstrated in the general human population (79), one may anticipate that

517 individuals bearing the HLA-DRB1 1501 allele exhibit functional specificities regarding their
518 anti-Tau T-cell responses.

519 We previously proposed that the genetic polymorphism of the HLA-DRB1 locus,
520 which, among primates, is extremely high in the human species (107), might allow the allele-
521 specific presentation of distinct sets of “brain superautoantigens” (108,109) leading, in turn,
522 to the development and maintenance of distinct sets of cognition-promoting T-cells. The
523 present work indicates that common neurodegeneration-associated proteins might
524 represent an important share of brain superautoantigens. Interestingly, recent magnetic
525 resonance imaging studies reported that, in healthy subjects, specific HLA-DR alleles
526 correlate with the volume ranges of specific brain structures (110,111). Future studies
527 should be designed to determine whether HLA-DR polymorphism might match both brain
528 structural features and the diversity of T-cell responses against common neurodegeneration-
529 associated proteins. Finally, in the human B-cell lineage, MHC class II-binding endogenous
530 peptides are highly significantly and specifically enriched in peptides deriving from common
531 neurodegeneration-associated proteins. This result raises the intriguing possibility that a
532 main function of physiological autoimmunity could be to control the blood-circulating levels
533 of aggregated forms of amyloid beta A4 protein, alpha-synuclein, tau protein and possibly
534 other neurodgeneration-associated proteins.

535

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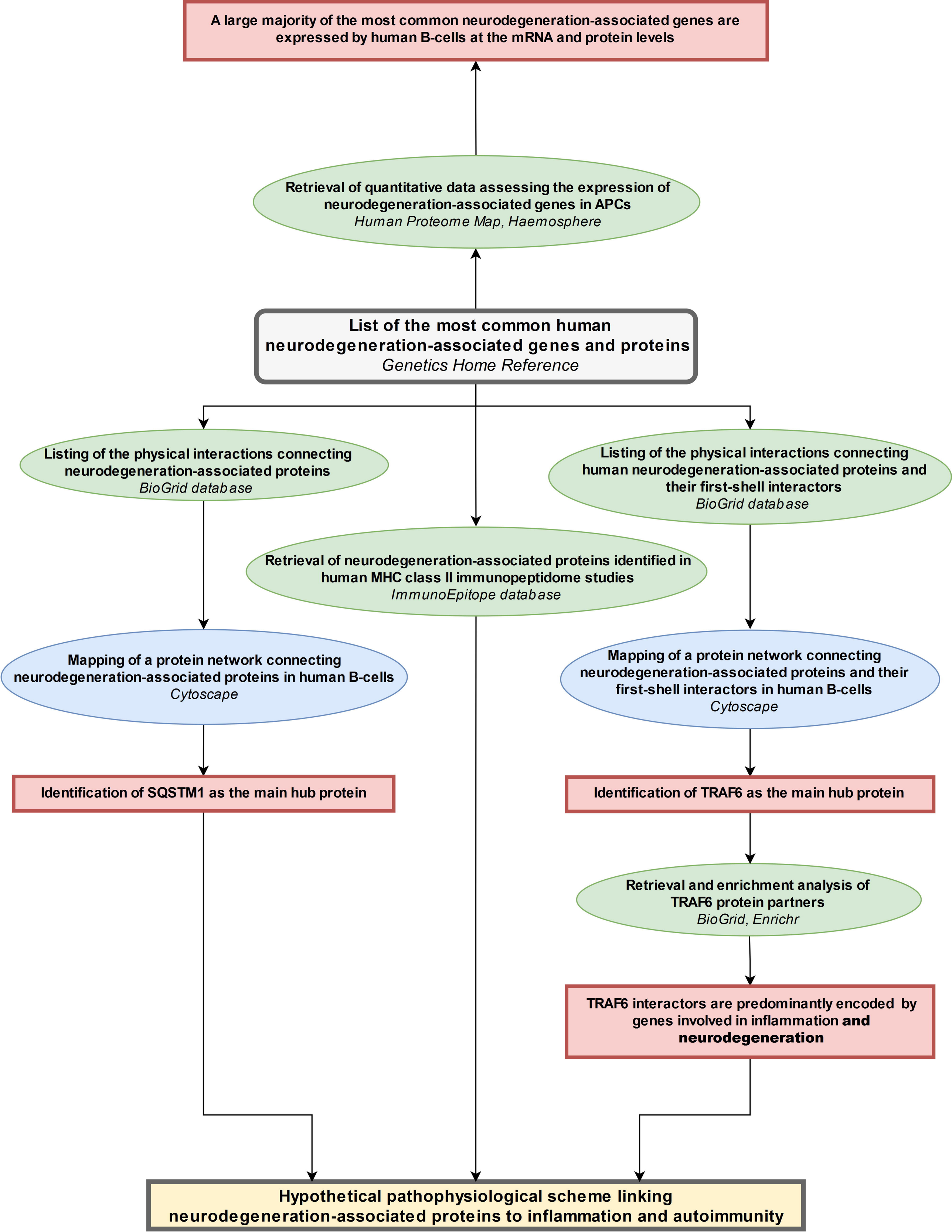
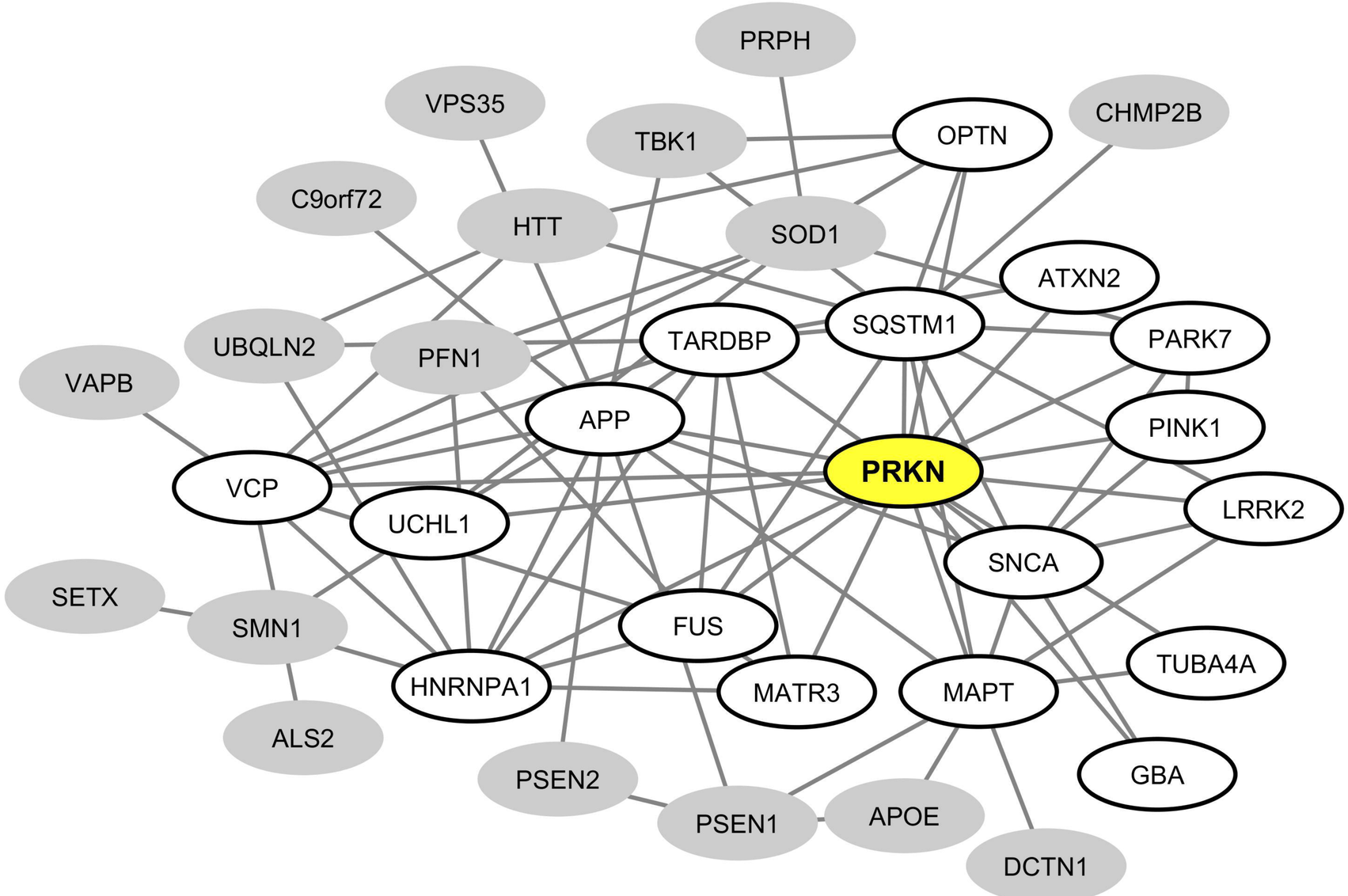

A large majority of the most common neurodegeneration-associated genes are expressed by human B-cells at the mRNA and protein levels
Retrieval of quantitative data assessing the expression of neurodegeneration-associated genes in APCs
Human Proteome Map, Haemosphere
List of the most common human neurodegeneration-associated genes and proteins
Genetics Home Reference
Listing of the physical interactions connecting neurodegeneration-associated proteins
BioGrid database
Listing of the physical interactions connecting human neurodegeneration-associated proteins and their first-shell interactors
BioGrid database
Retrieval of neurodegeneration-associated proteins identified in human MHC class II immunopeptidome studies
ImmunoEpitope database
Mapping of a protein network connecting neurodegeneration-associated proteins in human B-cells
Cytoscape
Mapping of a protein network connecting neurodegeneration-associated proteins and their first-shell interactors in human B-cells
Cytoscape
Identification of SQSTM1 as the main hub protein
Identification of TRAF6 as the main hub protein
Retrieval and enrichment analysis of TRAF6 protein partners
BioGrid, Enrichr
TRAF6 interactors are predominantly encoded by genes involved in inflammation and neurodegeneration
Hypothetical pathophysiological scheme linking neurodegeneration-associated proteins to inflammation and autoimmunity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TARDBP
VAPB
APP
PINK1
PRKN
VCP
LRRK2
UCHL1
SNCA
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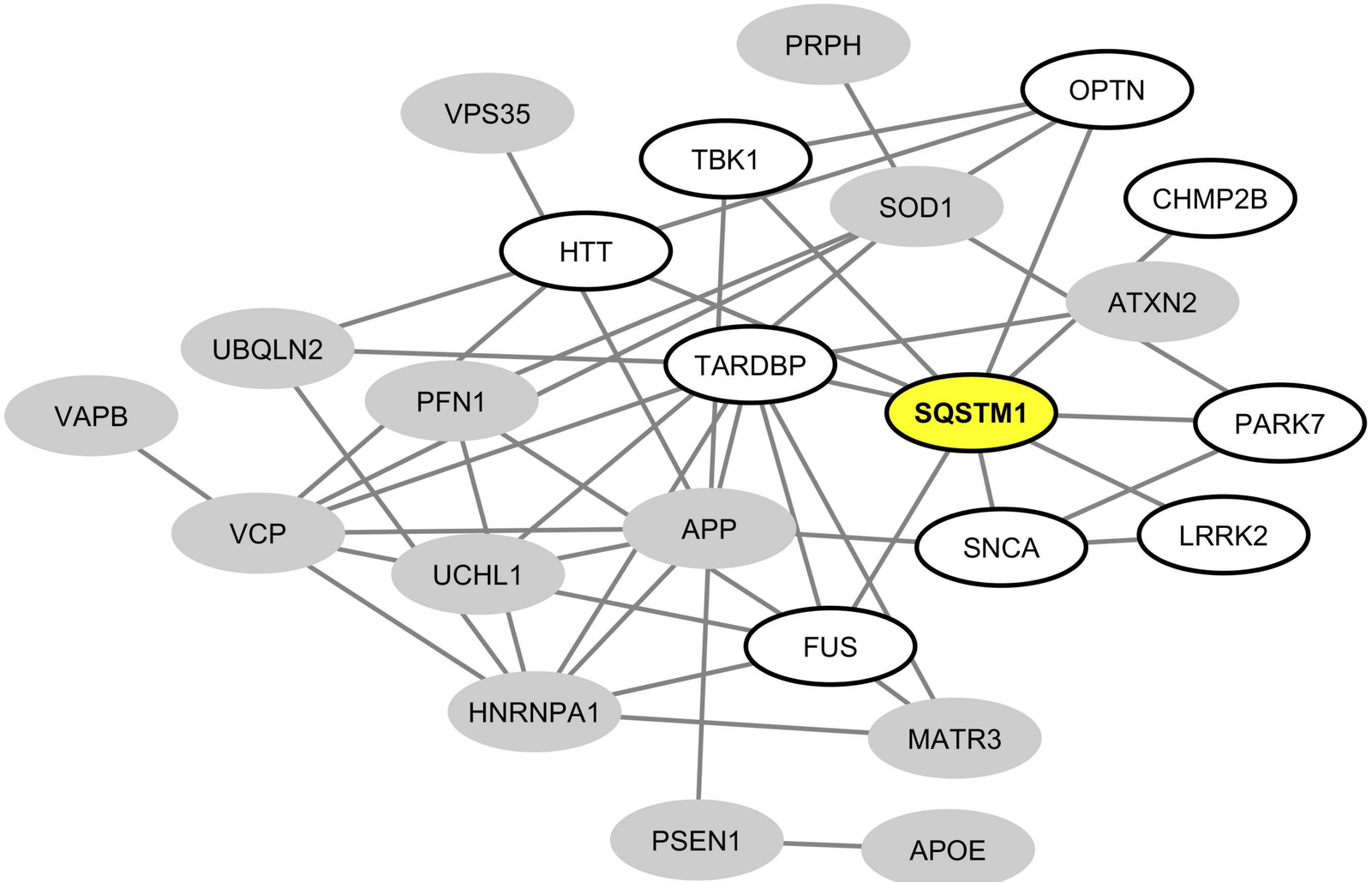
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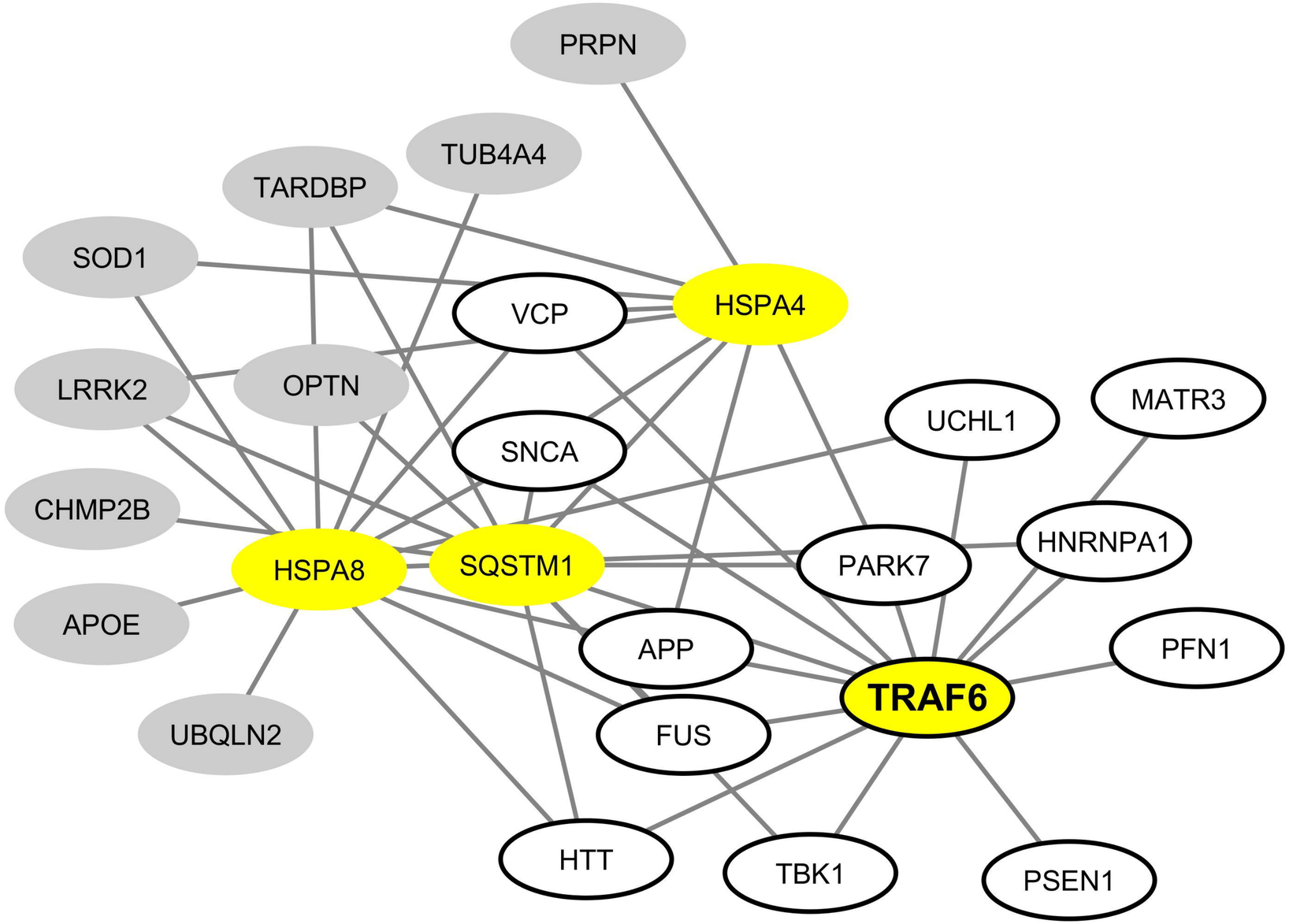
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