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Research Paper

Primate differential redoxome (PDR) – A paradigm for understanding neurodegenerative diseases

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ABSTRACT

Despite different phenotypic manifestations, mounting evidence points to similarities in the molecular basis of major neurodegenerative diseases (ND). CNS has evolved to be robust against hazard of ROS, a common perturbation aerobic organisms are confronted with. The trade-off of robustness is system's fragility against rare and unexpected perturbations. Identifying the points of CNS fragility is key for understanding etiology of ND. We postulated that the 'primate differential redoxome' (PDR), an assembly of proteins that contain cysteine residues present only in the primate orthologues of mammals, is likely to associate with an added level of regulatory functionalities that enhanced CNS robustness against ROS and facilitated evolution. The PDR contains multiple deterministic and susceptibility factors of major ND, which cluster to form coordinated redox networks regulating various cellular processes. The PDR analysis revealed a potential CNS fragility point, which appears to associates with a non-redundant PINK1-PRKN-SQSTM1(p62) axis coordinating protein homeostasis and mitophagy.

1. Introduction

Neurodegenerative diseases (ND) are characterized by progressive damage to neurons resulting in compromised cognitive and/or motor functions. The most common Alzheimer's and Parkinson's diseases affect 10 and 2%, respectively, of the USA population above age of 65 [1]. While, according to the current level of understanding, the vast majority of ND are sporadic, heredity plays an important role, with genetic effects ranging from deterministic, caused by highly penetrant monogenic mutations (less than 1% of cases) to common susceptibility factors (usually in the odds ratio range of 1.0–1.4) [2]. Although a multitude of susceptibility variants have been identified, they only explain a small fraction of the heritable risk, the so-called 'missing heritability' problem [2–4]. The missing heritability could be explained by assuming strong gene–gene and gene–environment interactions, in which subsets of genetic variants affect disease risk only in certain combinations or under certain pathophysiological circumstances [2]. Age is an important risk factor for ND, while other risk factors associate with general lifestyle and improper management of various health conditions, in particular cardiovascular and metabolic diseases, and head injury [5]. Despite advancements in the field, our level of understanding ND etiology is insufficient to enable causal therapy for most ND.

Being natural products of metabolic activity, reactive oxygen species (ROS) are not merely malevolent molecules, they carry out important signaling functions, such as mediating inflammatory responses, regulating the processes of cell survival and responses to various stresses [6–8]. Uncontrolled ROS production, however, has been associated with

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pathogenesis of common diseases, including cardiovascular, muscle dysfunction, allergy and cancers [1]. Mounting evidence assigns ROS, if not a causative, but exacerbating role in neurotoxicity; elevated levels of ROS are commonly found in the nervous tissues of ND patients [1,9,10]. Neuron cells are especially susceptible to oxidative damage due to their high metabolic rate, relatively inefficient antioxidant system and high membrane content of oxidation-prone polyunsaturated fatty acids [11]. The two marked attributes of ND, inflammatory response and mitochondrial dysfunction, are being linked to the increased ROS production and oxidative stress [1].

Sulfhydryl is a highly reactive chemical group and its presence in a surface-exposed unprotected form is an evolutionary drawback; it renders proteins vulnerable to oxidative damage, including irreversible oxidation to sulfonic acid ($R–SO_3H$) and the formation of intermolecular disulfides leading to aggregation. The conservation of exposed cysteines throughout evolution is an indication of their functional importance [12]. Indeed, reversible cysteine oxidation, *e.g.*, the sulfenic (R–SOH) or sulfinic ($R–SO_2H$) switches, is known to facilitate redox sensing and signaling by modifying various protein properties including activity, interaction with other proteins, cellular localization and turnover [6,13–19].

The CNS of the organisms, which have reached the top of the evolutionary ladder, such as primates, coordinate extremely complex mental and physical activities, and could be regarded, in evolutionary sense, the most prominent physiological/biochemical advance that facilitated separation of primates from other mammals. We, therefore, hypothesized that the biochemical fingerprints found exclusively in the primate orthologues of mammals, may associate, with a high likelihood, with CNS functions. We thus assumed that a human sub-proteome comprising proteins that contain non-conserved cysteines unique to the primate orthologues, the so-called 'primate differential redoxome' or PDR, is likely to associate with CNS redox homeostasis and ROS management. While there is a general tendency to lose cysteines (due to their chemical reactivity), evolution is still free to explore a path wherein adding thiols confers ROS signaling possibilities that underlie greater plasticity and robustness [12]. The downside of such arrangement, however, is that 'over-adapted' organisms become fragile and susceptible to oxidative stress when redox signaling fails [12,20]. This trait cannot be 'selected out' by evolution since CNS diseases generally happen late in life (after reproduction period). Thus, the gain early in life comes at a cost later in life. Identifying the points of CNS fragility may hold key to understanding ND pathogenesis. Here, we demonstrated that a multitude of deterministic and susceptibility factors of common ND are components of the PDR, where they cluster to form coordinated redox networks regulating various cellar processes. The PDR analysis led to the identification of a potential point of CNS fragility, which under certain pathophysiological circumstances may lead to ND.

2. Results and discussion

We postulated that the PDR derived from the whole human proteome is associated, in its majority, with CNS functions. However, focusing on a much smaller sub-PDR of the proteome of CNS disorders is an advantage, because it covers, with a high probability, the processes underlying CNS fragility. To define the PDR of CNS disorders, we devised an automatic protocol (see Methods) to analyze a dataset of human proteins linked to common CNS disorders to retrieve proteins that contain non-conserved cysteines present only in the primate orthologues of mammals (the software for analysis is available at: https://github.com/Engel-Lab/PDR). The following sources were used to compile the dataset: 1) Reviewed human sequences from the Uniprot database [21] retrieved using the following filters: amyotrophic lateral sclerosis (ALS); Alzheimer; autism; bipolar disorder; central nervous system; central nervous system disease; dementia; Huntington; mental disease; multiple sclerosis; neurodegeneration; Parkinson; schizophrenia. 2) Mass spectrometry study of ND proteomics [22], 3) GWAS studies of Alzheimer's [23,24], Parkinson's [25] and Huntington's [26] diseases, ALS [4,27] and frontotemporal dementia (FTD) [28]. Collectively, we analyzed 2040 non-redundant human protein sequences. On average, 16% (328) of the analyzed proteins contained one or more cysteines unique to primates. The analysis of a subset of hit proteins, for which experimental structural data were available, revealed that in a vast majority of cases, the unique cysteine residues were surface-exposed (not shown), indicating their susceptibility to oxidation. The resulting PDR contained products of prominent deterministic and susceptibility genes of major ND (Table 1, and Supplementary Table S1. The following are some examples:

2.1. Alzheimer disease (AD)

Out of 307 proteins analyzed in association with AD, 43 (14%) contained putative regulatory cysteines. Among them:

APOE (*APOE*)-Apolipoprotein E is a major component of lipoprotein complex involved in lipid metabolism and transport [29]. Of the three polymorphic forms of *APOE*, namely *APOE2*, *APOE3* and *APOE4*, *APOE4* increases risk of AD (including early-onset AD), while *APOE2* is protective [30,31]. *APOE4* is also a risk factor for other ND, including cerebral amyloid angiopathy (CAA), dementia with Lewy bodies (DLB), tauopathy, cerebrovascular disease, multiple sclerosis, and vascular dementia, and being related to poor outcome after traumatic head injury [30,31]. Strikingly, APOE4 differs from benign APOE isoforms by a substitution of the putative regulatory Cys^{129} for Arg.

PRIO (*PRNP*)-Prion protein (PrP), whose abnormal (misfolded) versions are responsible for a multitude of ND, including Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia. Some PrP mutations were suggested to associate also with Alzheimer's type pathology, spongiform encephalopathy and FTD [32–34].

FLNA (*FLNA*) – filamin A, an ubiquitous scaffolding protein, whose abnormal forms are critically linked to tau pathologies in AD [35]. A small molecule that binds misfolded FLNA to restore its native conformation is being considered as a drug candidate to treat AD [36].

SQSTM1 (*SQSTM1*)-Sequestosome-1 (p62), a stress-responsive ubiquitin-binding selective autophagy receptor involved in proteasome-dependent degradation of proteins and autophagy. Causal relationships have been found between p62 dysregulation and ND, including AD, PD, HD, ALS [both familial (fALS) and sporadic (sALS)] and FTD. p62 is commonly found in neuronal and glial ubiquitin-positive inclusions in AD, PD and Pick diseases, dementia with Lewy bodies, multiple system atrophy, SOD1-positive fALS and other forms of ALS (sALS, non-SOD1 fALS, and ALS with dementia) [37–40].

NLRP3 (*NALP3*)-NACHT, LRR and PYD domains-containing protein 3, also known as cryopyrin, a component of the inflammasome. Chronic low-level activation of NLRP3 inflammasome by amyloid β (Aβ), aggregated α-synuclein, ROS, and disrupted mitophagy is known to promote ND, such as AD and PD, by triggering the release of proinflammatory cytokines, leading to neuroinflammation and pyroptotic cell death in various brain regions [41–43].

About half of the risk gene candidates identified by GWAS of AD [23,24] encode for proteins containing putative regulatory cysteines; among them *ABCA7*, one of the most prominent risk genes of both early- and late-onset AD [44,45]. Others are M4A6A (*MS4A6*A), CASS4; DSG2; RIN3; SHIP1 (*INPP5D*) and TXND3 (*NME8*) [23].

2.2. Parkinson disease (PD)

Out of 172 proteins analyzed in association with PD, 35 (20%) contained putative regulatory cysteines. Among them:

PRKN (*PARK2*, Parkin)-E3 ubiquitin ligase Parkin is involved in mitochondrial maintenance and proteasome-dependent degradation of proteins [46]. Pathogenic variants of *PARK2* cause parkin-type early-onset autosomal recessive PD (ARPD); heterozygotes may have

Table 1
Sub-PDR associated with Alzheimer's (AD), Parkinson's (PD), Amyotrophic lateral sclerosis (ALS) and Huntington's (HD) diseases. Gene names are used; numbers correspond to the position(s) of non-conserved cysteine(s) in the human query sequence (as they appear in Uniprot database).

AD		PD		ALS		HD	
Gene name	**Cys No.**	**Gene name**	**Cys No.**	**Gene name**	**Cys No.**	**Gene name**	**Cys No.**
AATF	71	ATP10A	616, 931, 1317	CHRNB4	365	SH3BP2	259, 266, 314
ABCA7	785	BCKDK	110	ALS2	876	CARD16	104
ABI3	136	DNAJC13	2180	BPTF	1356	FAM193A	1185, 1195
APBA3	301, 375	POLG	532	CASP10	96	FAN1	792
APBB3	230	FBXO7	35	CCNF	770	HTT	1440
APOE	129	MTFMT	36	CDK15	78	HIP1	825
ASAH2	709	FOXRED1	115	CFAP410	158	MTMR10	411
BPTF	1356	PDDC1	153	DNAJB2	242	PRNP	5
CALHM3	320	GDI1	393	FLACC1	414	SETD2	301, 1935
CADPS2	555	HLA-B	331, 348	ICA1L	424	SQSTM1	26
CASS4	8	INPP5B	161	KIR3DL2	301, 335	TAF1	4
CTSD	11	ITGA8	35	NBEAL1	143, 1558	ZDHHC13	446
C20orf203	160	LRRK1	80, 362, 438, 1532, 1577, 1723	NEK1	1178	ZNF395	130, 437
DPYSL2	178	MCCC1	128, 331	OMA1	370		
DSG2	870	NBEAL2	120	PARD3B	633		
CES1	389	POR	433	PON3	219		
FLNA	2542	NDUFA9	27, 32	SETX	1228		
FRIH	90	NDUFB8	143	SOD1	111		
GSAP	384	NDUFAF5	10	SQSTM1	26		
HSD17B10	213	NDUFS6	13	TRAK2	168, 857		
CAST	407	NLRP3	195, 462				
CAMKK2	564	NOS2	525, 578				
MS4A6A	239	PIK3C2A	540				
CDC25B	19	PDE8B	107				
CDC25C	256, 389	PIEZO1	49				
NLRP3	195, 462	PINK1	39, 91, 547				
NUMB	411	PLA2G6	145, 413				
PIEZO1	49	PARK2	94				
PRNP	5	SQSTM1	26				
PTPA	90, 93, 102	SREBF1	897, 931				
RIN3	291, 941	TFB2M	41				
INPP5D	955	TMEM175	16, 31, 456				
SPHK2	512	VPS13C	888, 1371, 2439, 3665				
SQSTM1	26	FAM21C	827				
STH	9	DFNB31	615				
SV2C	716						
THOP1	349, 688						
TMF1	856						
TSHZ1	162						
TSHZ3	68, 497						
TTC3	155, 2021						
NME8	147, 207						
SLC30A6	145						

increased susceptibility to late-onset disease [47].

PINK1 (*PINK1*)-PTEN-induced putative kinase 1 is involved in mitochondrial quality control by regulating Parkin activity via phosphorylation. Numerous mutations in *PINK1* are associated with a phenotype similar to that of ARPD with *PRKN* mutations. The mitochondrial PINK1 detects mitochondrial dysfunction, recruits cytoplasmic Parkin to ubiquitinate the damaged mitochondria and facilitate their removal by autophagy [48].

PLPL9 (*PLA2G6*)-Calcium-independent phospholipase A2 beta ($iPLA_2\beta$) involved in membrane homeostasis, fatty acid oxidation, autophagy and mitochondrial function. PLA2G6 dysfunction causes PLA2G6-associated neurodegenerations (PLAN), including infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), and PLA2G6-related autosomal recessive dystonia-parkinsonism. Mutations in *PLA2G6* are also associated with atypical autosomal recessive parkinsonism, and sporadic early-onset PD [49].

About third of the risk gene candidates identified by GWAS of PD [25] encode for proteins containing putative regulatory cysteines, namely BCKD (*BCKDK*), HLAB (*HLA-B*), ITA8, MCCA, SRBP1, TM175 (*TMEM175*) and VP13C (*VPS13C*).

2.3. Amyotrophic lateral sclerosis (ALS)

Out of 110 proteins analyzed in association with ALS, 20 (18%) contained putative regulatory cysteines. Among them:

SODC (*SOD1*)-ubiquitous Cu/Zn-superoxide dismutase is a superoxide detoxifying enzyme in cytoplasm. Numerous mutations in *SOD1* cause fALS in autosomal dominant manner [50], while mounting evidence indicates the involvement of misfolded $SOD1^{WT}$ in sALS [12]. Non-conserved surface-exposed Cys^{111} is extremely oxidation-prone [51–53], and has long been considered a potential player in ALS pathogenesis. Cys^{111} oxidation was shown to promote the loss of the stabilizing metal cofactors, leading to misfolding and amyloid aggregation [54,55]. In cellular studies, the replacement of Cys^{111} by Ser or Ala was reported to ameliorate aggregation, mitochondrial accumulation and toxicity of misfolded fALS SOD1 mutants [56–59], and $SOD1^{H46R/C111S}$ double mutant demonstrated delayed disease onset and progression in transgenic ALS model mice [60].

ALS2 (*ALS2*)-Alsin, a guanine nucleotide exchange factor for small GTPase Rab5 abundant in motor neurons, is involved in membrane organization, endosomal trafficking and neurite outgrowth. Mutations in *ALS2* cause juvenile-onset fALS and infantile Henoch-Schonlein Purpura (HSP) [61]. ALS2 and SQSTM1 have been shown to impose additive protective effects against mutant SOD1-mediated toxicity by modulating

neuronal proteostasis via autophagy-endolysosomal system [62].

SETX (*SETX, ALS4*)-ubiquitously expressed Senataxin involved in transcriptional regulation. Mutations in SETX cause a rare, childhood or adolescent-onset autosomal dominant form of ALS, which is characterized by slow disease progression without implicating respiratory musculature [63,64].

2.4. Huntington disease (HD)

Out of 63 proteins analyzed in association with HD, 13 (21%) contained putative regulatory cysteines. Among them:

HD (*HTT*)-Huntingtin, a ubiquitous scaffolding protein controlling a wide variety of cellular processes, including the trafficking of vesicles and organelles in axons and dendrites, ciliogenesis, endocytosis, vesicle recycling, endosomal trafficking, and autophagy [65]. The mutation responsible for HD is an abnormal expansion of a CAG repeat in *HTT* gene, but it's unclear whether gain- or loss-of-function is responsible for toxic effects. HD regulates cargo recognition in autophagy by interacting with autophagy receptor p62 (SQSTM1), whereas both loss of *HTT* and polyQ expansion lead to impaired cargo recognition and the formation of empty autophagosomes [66].

FAN1 (*FAN1*)-GWAS identified FANCI-associated nuclease 1 (FAN1)

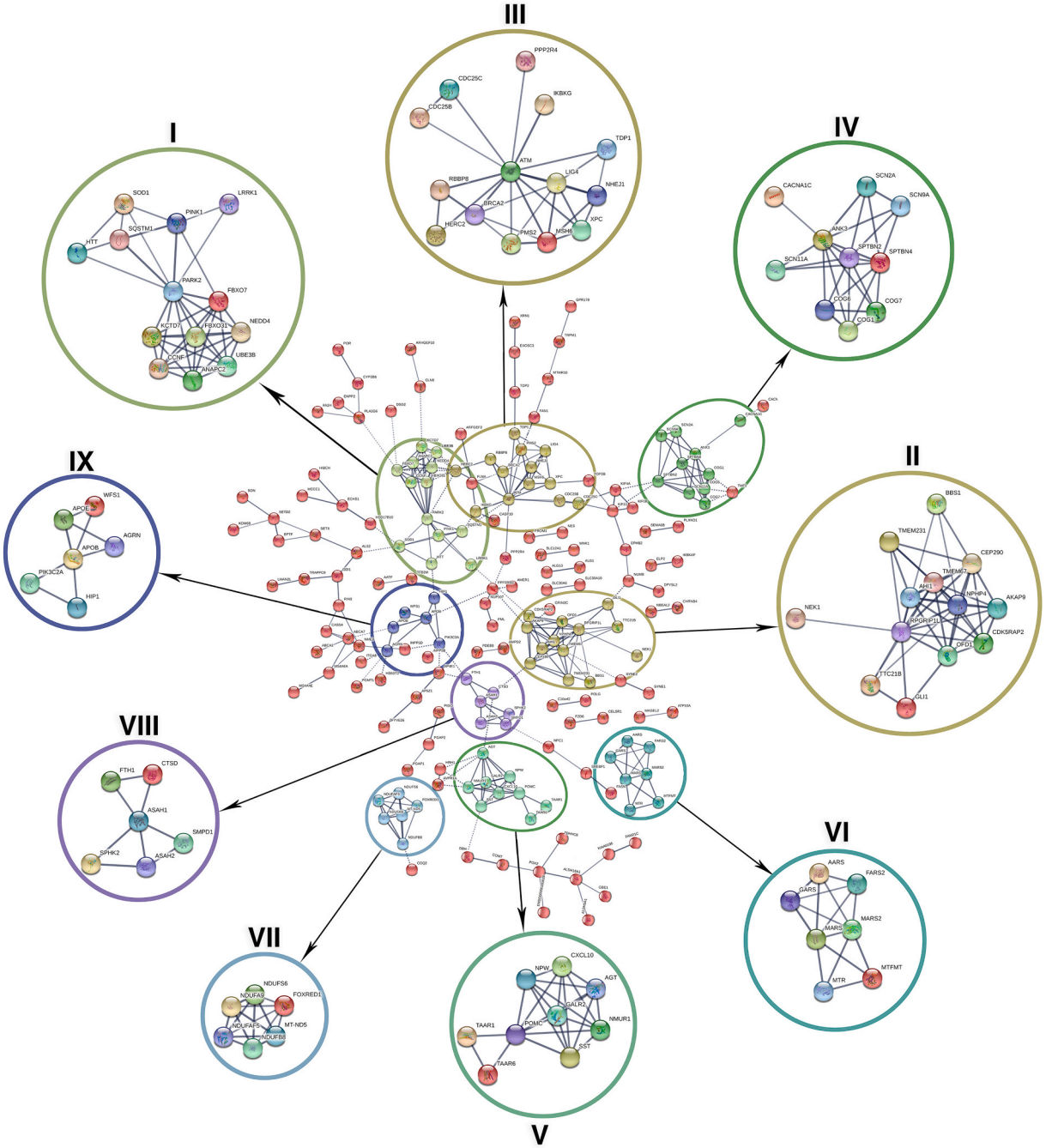

Fig. 1. PDR components form coordinated redox networks (clusters). The PDR of CNS disorders comprising 328 non-redundant human proteins was mapped onto a human PPI network (STRING, see Methods). Disconnected nodes were omitted for simplicity; weakly connected nodes are colored in red. k-means clustering was used to generate nine clusters of the closest associations. The cluster proteins were analyzed for enriched functions using GO:Biological Process analysis. The detailed description of the clusters appears in Table 2 and Supplementary Fig. S1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

involved in DNA repair as a risk gene for HD [26]. Increased *FAN1* expression is associated with delayed onset and slower disease progression in HD patients. It was suggested that FAN1, acting in concert with other DNA damage response (DDR) proteins, stabilizes the CAG repeat region of *HTT* and thus modulates HD pathogenesis [67].

Although our analysis was limited to the proteome of CNS disorders, we reckon that a similar abundance of proteins with unique cysteines would be found throughout the entire human proteome. Any other outcome would imply a causative relationship between the failure of the redox-sensing mechanisms and ND pathogenesis, which we deemed as unlikely on the basis of evolutionary and system biology considerations.

As the most evolved biological system, primate CNS is highly robust to cope with common perturbations [20,68]. Robustness enables evolution to explore new phenotypes and unoccupied niches without lethal effects, therefore robustness is requisite to evolvability [20,68,69]. Being evolved in aerobic atmosphere, the most common perturbation encountered by living organisms is hazard of ROS, and CNS, because of its high metabolic rates, is at the highest risk of oxidative damage. Without effective management of ROS, evolution of early mammal CNS to highly sophisticated and versatile primate CNS would not have been possible. We thus hypothesized that the PDR is part of a redox control mechanism emerged to enhance robustness of primate CNS against ROS. In addition to redox-sensing, surface-exposed cysteines may act as 'passive' redox tags, whose irreversible oxidation marks proteins for degradation, thus furnishing a redox surveillance protocol to maintain a healthy pool of key proteins under changing metabolic circumstances. Assuming robustness of primate CNS against ROS, we argue that redox disbalance-a common manifestation of ND-is insufficient, on its own right, to trigger ND. We may find support to this claim in the fact that G6PD-deficiency does not significantly increase risk of neurodegeneration in affected individuals [70]. This is due to the ability of the nervous tissue to compensate for the deficiency of pentose phosphate pathway in cytoplasm with the mitochondrial pathways to regenerate NADPH [71], a manifestation of the system's adaptability and robustness against ROS.

We next mapped the PDR onto a human protein-protein interaction (PPI) network (STRING PPI Networks and Functional Enrichment Analysis) [72] to identify incidences of coordinated redox regulations in proteins involved in common biological processes [6]. Although the majority of the PDR components were only weakly connected, we identified a number of well-defined clusters carrying out diverse biological activities (Fig. 1, Table 2, Supplementary Fig. S1). The importance of these clusters is that they expose biological processes, which are likely to make a significant contribution to enhanced robustness of primate CNS against ROS. The first largest cluster (cluster I) was enriched in proteins involved in the regulation of ubiquitin-dependent catabolism of proteins, including all the crucial components of the homeostatic axis mediating proteasome-dependent protein degradation and mitochondrial clearance by autophagy (mitophagy), namely PINK1-PRKN-SQSTM1(p62) [46,73]. In damaged mitochondria, the loss of membrane potential results in the accumulation of PINK1, the membrane depolarization sensor, on the outer mitochondrial membrane (OMM). PINK1 in turn recruits the E3 ubiquitin ligase Parkin, which functions as signal amplifier via ubiquitination of various OMM proteins, which in turn are recognized by p62/SQSTM1, a selective autophagy receptor, which function as adaptor protein to recruit autophagosome to the damaged mitochondria [74].

This cluster also contained HD (HTT) and SOD1, prominent pathogenic proteins in HD and ALS, respectively. Both diseases are characterized by impaired autophagy [66,75–77], and HTT by itself is a known autophagy regulator [66,78]. The enhanced redox-sensitivity of the homeostatic axis may have a bolstering effect on the existing link between the quality control systems and redox state [79], facilitating evolution of primate CNS. Timely removal of oxidation-damaged proteins and malfunctioning mitochondria, a major source of ROS, would insure CNS robustness against oxidative self-destruction.

Table 2
Functional enrichment analysis of clusters shown in Fig. 1. The analysis was performed using g:Profiler (see Methods).

Cluster	PDR nodes (gene names)	Biological processes enriched	Description
I	*FBXO7, SOD1, KCTD7, FBXO31, ANAPC2, UBE3B, HTT, PARK2, PINK1, LRRK1, SQSTM1, CCNF, NEDD4*	Ubiquitin-dependent catabolism of proteins, proteasome-dependent protein degradation and mitochondrial clearance by autophagy (mitophagy)	https://biit.cs.ut.ee/gplink/l/d2Thvu-GT7
II	*GLI1, TTC21B, TMEM231, BBS1, CDK5RAP2, OFD1, AKAP9, AHI1, NPHP4, RPGRIP1L, TMEM67, NEK1, CEP290*	Regulation of cilium assembly	https://biit.cs.ut.ee/gplink/l/p2_WY4YER9
III	*MSH6, CDC25B, HERC2, PMS2, ATM, XPC, CDC25C, TDP1, NHEJ1, BRCA2, PPP2R4, RBBP8, IKBKG, LIG4*	Response to DNA damage stimuli, DNA repair and nucleic acid metabolism	https://biit.cs.ut.ee/gplink/l/N5gF9ETfQ1
IV	*SPTBN4, CACNA1C, ANK3, COG1, COG7, SCN11A, SCN2A, SCN9A, COG6, SPTBN2*	Transmission of nerve impulse by regulating transmembrane ion transport and vesicle-mediated ER to Golgi transport	https://biit.cs.ut.ee/gplink/l/7NtlHP5MSX
V	*TAAR6, TAAR1, SST, CXCL10, NMUR1, GALR2, NPW, AGT, POMC*	GPCR-mediated signal transduction by neuropeptides	https://biit.cs.ut.ee/gplink/l/LpyETbSZTY
VI	*MTFMT, AARS, MARS, MARS2, FARS2, MTR, GARS*	Biosynthesis and metabolism of aminoacyl-tRNA	https://biit.cs.ut.ee/gplink/l/JGvzm8HCSY
VII	*FOXRED1, NDUFA9, NDUFS6, NDUFB8, MT-ND5, NDUFAF5*	Oxidative phosphorylation and thermogenesis	https://biit.cs.ut.ee/gplink/l/M7UAbg3GSy
VIII	*CTSD, SPHK2, FTH1, SMPD1, ASAH1, ASAH2*	Metabolism of sphingolipids and ceramides	https://biit.cs.ut.ee/gplink/l/ChchRS3qRs
IX	*WFS1, APOB, APOE, PIK3C2A, HIP1, AGRN*	Control of membrane organization, endocytosis, phospholipid and cholesterol transport and metabolism.	https://biit.cs.ut.ee/gplink/l/H2IBRNCeTV

The second largest cluster (cluster II) was enriched in proteins regulating cilium assembly. This is an intriguing finding, since there has been growing recognition of cilium, acting as a sensory platform, to be involved in the regulation of autophagy in response to a variety of extracellular stimuli [80–82]. HD is characterized by defective cilia structure and impaired autophagy, suggesting a potential link between cilia, autophagy and HD pathogenesis [83]. Chronic inflammation may elevate extracellular ROS [84,85], with a potential of damaging cells from outside and also, by diffusing through the membrane, from inside. Regulation by redox cues endows cilia with a capability of monitoring cellular surroundings for elevated ROS, priming the protein homeostatic system for forthcoming oxidative insult, thus further enhancing robustness of primate CNS against ROS.

The third largest cluster (cluster III) was enriched in proteins involved in the response to DNA damage stimuli, DNA repair and nucleic acid metabolism. The ability to maintain genomic integrity is principal for long-living postmitotic cells, such as neurons, which are mostly irreplaceable and rely on their genetic content for the entire lifespan of the organism [86]. Thus, according to the PDR, evolution of primate CNS was facilitated by genomic modifications that enhanced the synchronization between the DNA repair pathways and the redox state. The remaining clusters were enriched in proteins involved in the transmission of nerve impulse by regulating transmembrane ion transport and ER to Golgi vesicle-mediated transport (cluster IV); GPCR-mediated

signal transduction by neuropeptides (cluster V); aminoacyl-tRNA biosynthesis and metabolism (cluster VI); oxidative phosphorylation and thermogenesis (cluster VII); metabolism of sphingolipids and ceramides (cluster VIII); and control of membrane organization, endocytosis, phospholipid and cholesterol transport and metabolism (cluster IX, including APOE), Fig. 1, Table 2 and Supplementary Fig. S1.

Mutations (polymorphism) may interfere with the cysteine function as redox switches, either directly, as in APOE4, in which the putative regulatory cysteine was replaced by Arg, or indirectly, *e.g.*, by altering cysteine's reactivity/exposure [6]. However, the effect such mutations have on the functioning of CNS as whole is expected, due to the system's robustness, be minor. Yet, mutations may have a 'priming' effect, shifting the system toward a metastable state with an increased probability of collapse once perturbed in an unexpected way, explaining the paradigm of 'missing heritability' mentioned in the Introduction [2–4]. A principal trade-off of systems evolved to be robust against general perturbations, is their extreme fragility in the face of certain types of rare and unexpected perturbations [20,87], and thus ND can be seen as exposed fragility of CNS. Because fragility is a byproduct of robustness, the points of fragility are likely to associate with the mechanisms enhancing robustness [20]. Assuming that the PDR enhances CNS robustness against ROS, we conjectured that PDR analysis may provide important clues about the origin of CNS susceptibility to diseases.

Although robust systems are known to be rather tolerant to the removal of certain system components, fragility might be exposed if the system fails to eliminate components that behave improperly [20]. The vast majority of ND cases are sporadic. Irreversible post-translational modifications (PTM), *e.g.*, cysteine oxidation to sulfonic acid, may interfere with protein functions, but with a properly functioning homeostatic system they impose no threat because damaged proteins are timely eliminated. A failure to remove damaged proteins would result in their accumulation, 'upgrading' PTM to the level of mutations. The PDR revealed that in primates all the components of the protein homeostatic axis PINK1-PRKN-SQSTM1(p62) are equipped with extra cysteines, the transformation that increased susceptibility of the axis to oxidative damage. Since the axis maintains homeostasis of its own components [88–90], as well as keeps ROS production at bay by clearing malfunctioning mitochondria, it exists in a metastable state: a subtle deviation from its homeostatic steady-state may quickly propagate with an autocatalytic type of kinetics, resulting in a progressive loss of the axis's ability to maintain its own and cellular homeostasis, and enable unrestricted buildup of oxidative damage.

In a robust system, whose important characteristic is functional redundancy of the system components [20], metastability of a single component is insufficient to confer fragility. The structure of PDR cluster I, however, indicates that the metastable character of the homeostatic axis may indeed promote the formation of a potent fragility point in primate CNS (Fig. 1 and Supplementary Fig. S1). The cluster appears, at least in the PDR space, to have a bow-tie architecture, which is known to provide an advantage when a coordinated response to various stimuli is required [20]. A bow-tie architecture enhances robustness against external perturbations by allowing many inputs to be connected to a single robust core process. It also promotes evolvability, because as the genome size and complexity increase, new pathways can be added to the wings of the bow-tie without changing the overall configuration of the system [20]. The bow-tie structure of cluster I, however, suffers from a severe deficiency in the robustness of its core process, which is in fact represented by a single non-redundant component PRKN (Fig. 1 and Supplementary Fig. S1). The unbacked nature of the PRKN-mediated process is apparent from the deterministic character of *PARK2* mutations causing monogenic juvenile Parkinson disease in autosomal recessive manner [47]. The loss-of-function pathogenies suggests that PRKN is part of a non-redundant linear pathway, in which the failure of a single component results in a failure of the whole process. While evolution managed to promote CNS robustness against ROS by enhancing redox-sensitivity of the homeostatic axis (by adding reactive cysteines), it failed to provide a functional backup to the axis to compensate for its increasingly metastable character (due to the increased proneness to oxidative damage). Such evolutionary flaw produced a fragility point, whose risk of exposure rises with age, when the natural capacity of the homeostatic system to regenerate declines. As mentioned in the introduction, this evolutionary 'negligence' cannot be repaired, since ND generally happen after reproductive period.

An inevitable consequence of the homeostatic axis collapse would be increased oxidative stress. The phenotypic manifestation of such event, however, is expected to be tissue-specific. The cellular redoxome, due to its proneness to oxidation, would be among primary targets of uncontrolled ROS production. The susceptibility of the redoxome to oxidative damage, however, would depend on the pattern of PTM, *e.g.*, phosphorylation, prevalent in a given tissue [91]. Phosphorylation that occurs in the vicinity of a reactive cysteine residue may have a profound effect on its reactivity/exposure [6]. Thus, different subsets of redox-sensitive proteins are expected to be damaged in different tissues, giving rise to different phenotypic manifestations of disease.

In conclusion, in this work we conceptualized an inherent link between evolution in aerobic environment and susceptibility to ND. Moreover, the enduring unyielding challenge by ubiquitous ROS appears to be a factor that facilitated evolution of primate CNS. In this context, ND appears to be a genetically predetermined phenomenon originated from CNS over-fitting for survival amidst omnipresent ROS. The probability of the exposure of CNS fragility increases with age, therefore ND become progressively more common as the life expectancy rises. The effective ND treatment would require the very core of the CNS architecture to be amended, *e.g.*, by reinforcing the homeostatic axis by genetic manipulation. Finally, a potential pathogenic role of PDR dysfunction in ND raises important concerns regarding the validity of common *in vivo* models, *e.g.* rodent, lacking PDR, in studying the mechanism of ND.

3. Methods

3.1. PDR analysis

To construct PDR, we composed an automatic protocol, which performs the following tasks: (1) Submit a human protein sequence query to the BLAST server [92] to retrieve mammalian non-human orthologous that share at least 80% amino acid identity with the human query, to ensure that only highly homologues proteins are included in the analysis; (2) Align the query and the orthologues using the Muscle program for multiple sequence alignment [93]; (3) Analyze the aligned sequences for the presence of cysteines, and assign query to the PDR if it contains one or more cysteines present only in the primate aligned orthologues. At least 80% of the orthologues that contain cysteine in a given position are required to be primate, a tolerance adopted to avoid false-negatives caused by the presence of artificial (engineered) sequences retrieved by BLAST.

3.2. Protein-protein interaction Networks and Functional Enrichment Analysis

To define the biological function of the PDR components, the STRING database (version 11.0; http://string-db.org) was used to build and explore a high-confidence (>0.700) PPI network, in which edges represent specific and meaningful associations between proteins (*i.e.* the proteins jointly contribute to a shared function, but do not necessary physically bind each other). Data were unavailable for 6 proteins, 72 nodes were disconnected and 250 nodes form a major network. By using k-means clustering, nine clusters representing the closest associations were constructed for subsequent Gene Ontology:Biological Process analysis. The functional enrichment analysis for each cluster was performed using g:Profiler (version e99_eg46_p14_f929183; https://biit.cs.ut.ee/gprofiler/gost) with g:SCS multiple testing correction method

with a significance threshold of 0.05 [94]. Cytoscape 3.8.0 was used to visualize the network (https://cytoscape.org/).

Author contributions

S.E. conceived the original idea and wrote the manuscript; N.V. and S.B carried out the calculations and analyzed the results; D.E. composed the software for PDR analysis; Z.B. provided resources and contributed to the result analysis and writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2020.101683.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
CNS	Central nervous system
FTD	Frontotemporal dementia
GWAS	Genome-wide association study
HD	Huntington's disease
ND	Neurodegenerative diseases
PD	Parkinson's disease
PDR	Primate differential redoxome
PPI	Protein-protein interactions
PTM	Post-translational modification
ROS	Reactive oxidative species

References

[1] Z. Liu, T. Zhou, A.C. Ziegler, P. Dimitrion, L. Zuo, Oxidative Stress in Neurodegenerative Diseases: from Molecular Mechanisms to Clinical Applications, Oxidative Medicine and Cellular Longevity 2017, 2017, p. 2525967.
[2] L. Pihlstrøm, S. Wiethoff, H. Houlden, Chapter 22 - genetics of neurodegenerative diseases: an overview, in: G.G. Kovacs, I. Alafuzoff (Eds.), Handbook of Clinical Neurology, Elsevier, 2018, pp. 309–323.
[3] T.A. Manolio, F.S. Collins, N.J. Cox, D.B. Goldstein, L.A. Hindorff, D.J. Hunter, M. I. McCarthy, E.M. Ramos, L.R. Cardon, A. Chakravarti, J.H. Cho, A.E. Guttmacher, A. Kong, L. Kruglyak, E. Mardis, C.N. Rotimi, M. Slatkin, D. Valle, A.S. Whittemore, M. Boehnke, A.G. Clark, E.E. Eichler, G. Gibson, J.L. Haines, T.F.C. Mackay, S. A. McCarroll, P.M. Visscher, Finding the missing heritability of complex diseases, Nature 461 (2009) 747–753.
[4] R. Mejzini, L.L. Flynn, I.L. Pitout, S. Fletcher, S.D. Wilton, P.A. Akkari, ALS genetics, mechanisms, and therapeutics: where are we now? Front. Neurosci. 13 (2019).
[5] S. Pugazhenthi, L. Qin, P.H. Reddy, Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease, Biochimica et biophysica acta, Mol. Basis Dis. 1863 (2017) 1037–1045.
[6] H. Xiao, M.P. Jedrychowski, D.K. Schweppe, E.L. Huttlin, Q. Yu, D.E. Heppner, J. Li, J. Long, E.L. Mills, J. Szpyt, Z. He, G. Du, R. Garrity, A. Reddy, L.P. Vaites, J. A. Paulo, T. Zhang, N.S. Gray, S.P. Gygi, E.T. Chouchani, A quantitative tissue-specific landscape of protein redox regulation during aging, Cell 180 (2020) 968–983, e924.
[7] A. Mannaa, F.-G. Hanisch, Redox proteomes in human physiology and disease mechanisms, J. Proteome Res. 19 (2020) 1–17.
[8] L. Zuo, T. Zhou, B.K. Pannell, A.C. Ziegler, T.M. Best, Biological and physiological role of reactive oxygen species–the good, the bad and the ugly, Acta Physiol. 214 (2015) 329–348.
[9] V. Dias, E. Junn, M.M. Mouradian, The role of oxidative stress in Parkinson's disease, J. Parkinsons Dis. 3 (2013) 461–491.
[10] D.S. Albers, M.F. Beal, Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease, J. Neural. Transm. Suppl. 59 (2000) 133–154.
[11] A.C. Rego, C.R. Oliveira, Mitochondrial dysfunction and reactive oxygen species in excitotoxicity and apoptosis: implications for the pathogenesis of neurodegenerative diseases, Neurochem. Res. 28 (2003) 1563–1574.
[12] J.N. Cobley, M.L. Fiorello, D.M. Bailey, 13 reasons why the brain is susceptible to oxidative stress, Redox Biol. 15 (2018) 490–503.
[13] J.M. Held, Redox systems biology: harnessing the sentinels of the cysteine redoxome, Antioxidants Redox Signal. 32 (2020) 659–676.
[14] J. van der Reest, S. Lilla, L. Zheng, S. Zanivan, E. Gottlieb, Proteome-wide analysis of cysteine oxidation reveals metabolic sensitivity to redox stress, Nat. Commun. 9 (2018) 1581.
[15] L.A. Defelipe, E. Lanzarotti, D. Gauto, M.A. Marti, A.G. Turjanski, Protein topology determines cysteine oxidation fate: the case of sulfenyl amide formation among protein families, PLoS Comput. Biol. 11 (2015), e1004051.
[16] Z.A. Wood, L.B. Poole, P.A. Karplus, Peroxiredoxin evolution and the regulation of hydrogen peroxide signaling, Science 300 (2003) 650–653.
[17] S. Rahuel-Clermont, M.B. Toledano, Parsing protein sulfinic acid switches, Nat. Chem. Biol. 14 (2018) 991–993.
[18] S. Akter, L. Fu, Y. Jung, M.L. Conte, J.R. Lawson, W.T. Lowther, R. Sun, K. Liu, J. Yang, K.S. Carroll, Chemical proteomics reveals new targets of cysteine sulfinic acid reductase, Nat. Chem. Biol. 14 (2018) 995–1004.
[19] J.Y. Baek, S.H. Han, S.H. Sung, H.E. Lee, Y.-m. Kim, Y.H. Noh, S.H. Bae, S.G. Rhee, T.-S. Chang, Sulfiredoxin protein is critical for redox balance and survival of cells exposed to low steady-state levels of H2O2, J. Biol. Chem. 287 (2012) 81–89.
[20] H. Kitano, Biological robustness, Nat. Rev. Genet. 5 (2004) 826–837.
[21] T.U. Consortium, UniProt: a worldwide hub of protein knowledge, Nucleic Acids Res. 47 (2018) D506–D515.
[22] K.W. Li, A.B. Ganz, A.B. Smit, Proteomics of neurodegenerative diseases: analysis of human post-mortem brain, J. Neurochem. 151 (2019) 435–445.
[23] J.-C. Lambert, C.A. Ibrahim-Verbaas, D. Harold, A.C. Naj, R. Sims, C. Bellenguez, G. Jun, A.L. DeStefano, J.C. Bis, G.W. Beecham, B. Grenier-Boley, G. Russo, T. A. Thornton-Wells, N. Jones, A.V. Smith, V. Chouraki, C. Thomas, M.A. Ikram, D. Zelenika, B.N. Vardarajan, Y. Kamatani, C.-F. Lin, A. Gerrish, H. Schmidt, B. Kunkle, M.L. Dunstan, A. Ruiz, M.-T. Bihoreau, S.-H. Choi, C. Reitz, F. Pasquier, P. Hollingworth, A. Ramirez, O. Hanon, A.L. Fitzpatrick, J.D. Buxbaum, D. Campion, P.K. Crane, C. Baldwin, T. Becker, V. Gudnason, C. Cruchaga, D. Craig, N. Amin, C. Berr, O.L. Lopez, P.L. De Jager, V. Deramecourt, J.A. Johnston, D. Evans, S. Lovestone, L. Letenneur, F.J. Morón, D.C. Rubinsztein, G. Eiriksdottir, K. Sleegers, A.M. Goate, N. Fiévet, M.J. Huentelman, M. Gill, K. Brown, M. I. Kamboh, L. Keller, P. Barberger-Gateau, B. McGuinness, E.B. Larson, R. Green, A. J. Myers, C. Dufouil, S. Todd, D. Wallon, S. Love, E. Rogaeva, J. Gallacher, P. St George-Hyslop, J. Clarimon, A. Lleo, A. Bayer, D.W. Tsuang, L. Yu, M. Tsolaki, P. Bossù, G. Spalletta, P. Proitsi, J. Collinge, S. Sorbi, F. Sanchez-Garcia, N.C. Fox, J. Hardy, M.C.D. Naranjo, P. Bosco, R. Clarke, C. Brayne, D. Galimberti, M. Mancuso, F. Matthews, S. Moebus, P. Mecocci, M. Del Zompo, W. Maier, H. Hampel, A. Pilotto, M. Bullido, F. Panza, P. Caffarra, B. Nacmias, J.R. Gilbert, M. Mayhaus, L. Lannfelt, H. Hakonarson, S. Pichler, M.M. Carrasquillo, M. Ingelsson, D. Beekly, V. Alvarez, F. Zou, O. Valladares, S.G. Younkin, E. Coto, K. L. Hamilton-Nelson, W. Gu, C. Razquin, P. Pastor, I. Mateo, M.J. Owen, K.M. Faber, P.V. Jonsson, O. Combarros, M.C. O'Donovan, L.B. Cantwell, H. Soininen, D. Blacker, S. Mead, T.H. Mosley, D.A. Bennett, T.B. Harris, L. Fratiglioni, C. Holmes, R.F.A.G. de Bruijn, P. Passmore, T.J. Montine, K. Bettens, J.I. Rotter, A. Brice, K. Morgan, T.M. Foroud, W.A. Kukull, D. Hannequin, J.F. Powell, M. A. Nalls, K. Ritchie, K.L. Lunetta, J.S.K. Kauwe, E. Boerwinkle, M. Riemenschneider, M. Boada, M. Hiltunen, E.R. Martin, R. Schmidt, D. Rujescu, L.-S. Wang, J.-F. Dartigues, R. Mayeux, C. Tzourio, A. Hofman, M.M. Nöthen, C. Graff, B.M. Psaty, L. Jones, J.L. Haines, P.A. Holmans, M. Lathrop, M.A. Pericak-Vance, L.J. Launer, L.A. Farrer, C.M. van Duijn, C. Van Broeckhoven, V. Moskvina, S. Seshadri, J. Williams, G.D. Schellenberg, P. Amouyel, I. European Alzheimer's Disease, , Genetic, and Environmental Risk in Alzheimer's D., C. Alzheimer's Disease Genetic, H. Cohorts for, E. Aging Research in Genomic, Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease, Nat. Genet. 45 (2013) 1452–1458.
[24] P. Hollingworth, D. Harold, R. Sims, A. Gerrish, J.-C. Lambert, M.M. Carrasquillo, R. Abraham, M.L. Hamshere, J.S. Pahwa, V. Moskvina, K. Dowzell, N. Jones, A. Stretton, C. Thomas, A. Richards, D. Ivanov, C. Widdowson, J. Chapman, S. Lovestone, J. Powell, P. Proitsi, M.K. Lupton, C. Brayne, D.C. Rubinsztein, M. Gill, B. Lawlor, A. Lynch, K.S. Brown, P.A. Passmore, D. Craig, B. McGuinness, S. Todd, C. Holmes, D. Mann, A.D. Smith, H. Beaumont, D. Warden, G. Wilcock, S. Love, P.G. Kehoe, N.M. Hooper, E.R.L.C. Vardy, J. Hardy, S. Mead, N.C. Fox, M. Rossor, J. Collinge, W. Maier, F. Jessen, E. Rüther, B. Schürmann, R. Heun, H. Kölsch, H. van den Bussche, I. Heuser, J. Kornhuber, J. Wiltfang, M. Dichgans, L. Frölich, H. Hampel, J. Gallacher, M. Hüll, D. Rujescu, I. Giegling, A.M. Goate, J. S.K. Kauwe, C. Cruchaga, P. Nowotny, J.C. Morris, K. Mayo, K. Sleegers, K. Bettens, S. Engelborghs, P.P. De Deyn, C. Van Broeckhoven, G. Livingston, N.J. Bass, H. Gurling, A. McQuillin, R. Gwilliam, P. Deloukas, A. Al-Chalabi, C.E. Shaw, M. Tsolaki, A.B. Singleton, R. Guerreiro, T.W. Mühleisen, M.M. Nöthen, S. Moebus, K.-H. Jöckel, N. Klopp, H.E. Wichmann, V.S. Pankratz, S.B. Sando, J.O. Aasly, M. Barcikowska, Z.K. Wszolek, D.W. Dickson, N.R. Graff-Radford, R.C. Petersen, C. M. van Duijn, M.M.B. Breteler, M.A. Ikram, A.L. DeStefano, A.L. Fitzpatrick, O. Lopez, L.J. Launer, S. Seshadri, C. Berr, D. Campion, J. Epelbaum, J.-F. Dartigues, C. Tzourio, A. Alpérovitch, M. Lathrop, T.M. Feulner, P. Friedrich, C. Riehle, M. Krawczak, S. Schreiber, M. Mayhaus, S. Nicolhaus, S. Wagenpfeil,

S. Steinberg, H. Stefansson, K. Stefansson, J. Snædal, S. Björnsson, P.V. Jonsson, V. Chouraki, B. Genier-Boley, M. Hiltunen, H. Soininen, O. Combarros, D. Zelenika, M. Delepine, M.J. Bullido, F. Pasquier, I. Mateo, A. Frank-Garcia, E. Porcellini, O. Hanon, E. Coto, V. Alvarez, P. Bosco, G. Siciliano, M. Mancuso, F. Panza, V. Solfrizzi, B. Nacmias, S. Sorbi, P. Bossù, P. Piccardi, B. Arosio, G. Annoni, D. Seripa, A. Pilotto, E. Scarpini, D. Galimberti, A. Brice, D. Hannequin, F. Licastro, L. Jones, P.A. Holmans, T. Jonsson, M. Riemenschneider, K. Morgan, S.G. Younkin, M.J. Owen, M. O'Donovan, P. Amouyel, J. Williams, I. the Alzheimer's Disease Neuroimaging, C. consortium, E. consortium, Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease, Nat. Genet. 43 (2011) 429–435.

[25] M.A. Nalls, N. Pankratz, C.M. Lill, C.B. Do, D.G. Hernandez, M. Saad, A. L. DeStefano, E. Kara, J. Bras, M. Sharma, C. Schulte, M.F. Keller, S. Arepalli, C. Letson, C. Edsall, H. Stefansson, X. Liu, H. Pliner, J.H. Lee, R. Cheng, M.A. Ikram, J.P.A. Ioannidis, G.M. Hadjigeorgiou, J.C. Bis, M. Martinez, J.S. Perlmutter, A. Goate, K. Marder, B. Fiske, M. Sutherland, G. Xiromerisiou, R.H. Myers, L. N. Clark, K. Stefansson, J.A. Hardy, P. Heutink, H. Chen, N.W. Wood, H. Houlden, H. Payami, A. Brice, W.K. Scott, T. Gasser, L. Bertram, N. Eriksson, T. Foroud, A. B. Singleton, International Parkinson's Disease Genomics, C, Parkinson's Study Group Parkinson's Research: The Organized, G. I, Me, GenePd, NeuroGenetics Research, C, Hussman Institute of Human, G, The Ashkenazi Jewish Dataset, I, Cohorts for, H, Aging Research in Genetic, E, North American Brain Expression, C, United Kingdom Brain Expression, C, Greek Parkinson's Disease, C, Alzheimer Genetic Analysis, G, Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease, Nat. Genet. 46 (2014) 989–993.

[26] J.-M. Lee, Vanessa C. Wheeler, Michael J. Chao, Jean Paul G. Vonsattel, Ricardo M. Pinto, D. Lucente, K. Abu-Elneel, Eliana M. Ramos, Jayalakshmi S. Mysore, T. Gillis, Marcy E. MacDonald, James F. Gusella, D. Harold, Timothy C. Stone, V. Escott-Price, J. Han, A. Vedernikov, P. Holmans, L. Jones, S. Kwak, M. Mahmoudi, M. Orth, G.B. Landwehrmeyer, Jane S. Paulsen, E.R. Dorsey, I. Shoulson, Richard H. Myers, Identification of genetic factors that modify clinical onset of Huntington's disease, Cell 162 (2015) 516–526.

[27] I. Fogh, A. Ratti, C. Gellera, K. Lin, C. Tiloca, V. Moskvina, L. Corrado, G. Sorarù, C. Cereda, S. Corti, D. Gentilini, D. Calini, B. Castellotti, L. Mazzini, G. Querin, S. Gagliardi, R. Del Bo, F.L. Conforti, G. Siciliano, M. Inghilleri, F. Saccà, P. Bongioanni, S. Penco, M. Corbo, S. Sorbi, M. Filosto, A. Ferlini, A.M. Di Blasio, S. Signorini, A. Shatunov, A. Jones, P.J. Shaw, K.E. Morrison, A.E. Farmer, P. Van Damme, W. Robberecht, A. Chiò, B.J. Traynor, M. Sendtner, J. Melki, V. Meininger, O. Hardiman, P.M. Andersen, N.P. Leigh, J.D. Glass, D. Overste, F.P. Diekstra, J. H. Veldink, M.A. van Es, C.E. Shaw, M.E. Weale, C.M. Lewis, J. Williams, R. H. Brown, J.E. Landers, N. Ticozzi, M. Ceroni, E. Pegoraro, G.P. Comi, S. D'Alfonso, L.H. van den Berg, F. Taroni, A. Al-Chalabi, J. Powell, V. Silani, t.S. Consortium, Collaborators, V. Brescia Morra, A. Filla, F. Massimo, A. Marsili, P. Viviana, G. Puorro, V. La Bella, G. Logroscino, M.R. Monsurrò, A. Quattrone, I.L. Simone, K. B. Ahmeti, S. Ajroud-Driss, J. Armstrong, A. Birve, H.M. Blauw, L. Bruijn, W. Chen, M.C. Comeau, S. Cronin, G.A. Soraya, J.D. Grab, E.J. Groen, J.L. Haines, S. Heller, J. Huang, W.-Y. Hung, I. Consortium, J.M. Jaworski, H. Khan, C.D. Langefeld, M. C. Marion, R.L. McLaughlin, J.W. Miller, G. Mora, M.A. Pericak-Vance, E. Rampersaud, N. Siddique, T. Siddique, B.N. Smith, R. Sufit, S. Topp, C. Vance, P. van Vught, Y. Yang, J.G. Zheng, A genome-wide association meta-analysis identifies a novel locus at 17q11.2 associated with sporadic amyotrophic lateral sclerosis, Hum. Mol. Genet. 23 (2013) 2220–2231.

[28] R. Ferrari, D.G. Hernandez, M.A. Nalls, J.D. Rohrer, A. Ramasamy, J.B. Kwok, C. Dobson-Stone, W.S. Brooks, P.R. Schofield, G.M. Halliday, J.R. Hodges, O. Piguet, L. Bartley, E. Thompson, E. Haan, I. Hernandez, A. Ruiz, M. Boada, B. Borroni, A. Padovani, C. Cruchaga, N.J. Cairns, L. Benussi, G. Binetti, R. Ghidoni, G. Forloni, D. Galimberti, C. Fenoglio, M. Serpente, E. Scarpini, J. Clarimon, A. Lleo, R. Blesa, M.L. Waldo, K. Nilsson, C. Nilsson, I.R. Mackenzie, G.Y. Hsiung, D.M. Mann, J. Grafman, C.M. Morris, J. Attems, T.D. Griffiths, I.G. McKeith, A. J. Thomas, P. Pietrini, E.D. Huey, E.M. Wassermann, A. Baborie, E. Jaros, M. C. Tierney, P. Pastor, C. Razquin, S. Ortega-Cubero, E. Alonso, R. Perneczky, J. Diehl-Schmid, P. Alexopoulos, A. Kurz, I. Rainero, E. Rubino, L. Pinessi, E. Rogaeva, P. St George-Hyslop, G. Rossi, F. Tagliavini, G. Giaccone, J.B. Rowe, J. C. Schlachetzki, J. Uphill, J. Collinge, S. Mead, A. Danek, V.M. Van Deerlin, M. Grossman, J.Q. Trojanowski, J. van der Zee, W. Deschamps, T. Van Langenhove, M. Cruts, C. Van Broeckhoven, S.F. Cappa, I. Le Ber, D. Hannequin, V. Golfier, M. Vercelletto, A. Brice, B. Nacmias, S. Sorbi, S. Bagnoli, I. Piaceri, J.E. Nielsen, L. E. Hjermind, M. Riemenschneider, M. Mayhaus, B. Ibach, G. Gasparoni, S. Pichler, W. Gu, M.N. Rossor, N.C. Fox, J.D. Warren, M.G. Spillantini, H.R. Morris, P. Rizzu, P. Heutink, J.S. Snowden, S. Rollinson, A. Richardson, A. Gerhard, A.C. Bruni, R. Maletta, F. Frangipane, C. Cupidi, L. Bernardi, M. Anfossi, M. Gallo, M.E. Conidi, N. Smirne, R. Rademakers, M. Baker, D.W. Dickson, N.R. Graff-Radford, R. C. Petersen, D. Knopman, K.A. Josephs, B.F. Boeve, J.E. Parisi, W.W. Seeley, B. L. Miller, A.M. Karydas, H. Rosen, J.C. van Swieten, E.G. Dopper, H. Seelaar, Y. A. Pijnenburg, P. Scheltens, G. Logroscino, R. Capozzo, V. Novelli, A.A. Puca, M. Franceschi, A. Postiglione, G. Milan, P. Sorrentino, M. Kristiansen, H.H. Chiang, C. Graff, F. Pasquier, A. Rollin, V. Deramecourt, F. Lebert, D. Kapogiannis, L. Ferrucci, S. Pickering-Brown, A.B. Singleton, J. Hardy, P. Momeni, Frontotemporal dementia and its subtypes: a genome-wide association study, Lancet Neurol. 13 (2014) 686–699.

[29] R.W. Mahley, S.C. Rall Jr., Apolipoprotein E: far more than a lipid transport protein, Annu. Rev. Genom. Hum. Genet. 1 (2000) 507–537.

[30] C.-C. Liu, T. Kanekiyo, H. Xu, G. Bu, Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy, Nat. Rev. Neurol. 9 (2013) 106–118.

[31] M. Safieh, A.D. Korczyn, D.M. Michaelson, ApoE4: an emerging therapeutic target for Alzheimer's disease, BMC Med. 17 (2019) 64.

[32] L. Bernardi, A.C. Bruni, Mutations in prion protein gene: pathogenic mechanisms in C-terminal vs. N-terminal domain, a review, Int. J. Mol. Sci. 20 (2019).

[33] S.B. Prusiner, Genetic and infectious prion diseases, Arch. Neurol. 50 (1993) 1129–1153.

[34] W. Zhang, B. Jiao, T. Xiao, C. Pan, X. Liu, L. Zhou, B. Tang, L. Shen, Mutational analysis of PRNP in Alzheimer's disease and frontotemporal dementia in China, Sci. Rep. 6 (2016) 38435.

[35] C. Harrison, Targeting filamin A reduces Alzheimer's signalling, Nat. Rev. Drug Discov. 11 (2012), 674-674.

[36] H.-Y. Wang, K.-C. Lee, Z. Pei, A. Khan, K. Bakshi, L.H. Burns, PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiol. Aging 55 (2017) 99–114.

[37] E. Cuyvers, J. van der Zee, K. Bettens, S. Engelborghs, M. Vandenbulcke, C. Robberecht, L. Dillen, C. Merlin, N. Geerts, C. Graff, H. Thonberg, H.-H. Chiang, P. Pastor, S. Ortega-Cubero, M.A. Pastor, J. Diehl-Schmid, P. Alexopoulos, L. Benussi, R. Ghidoni, G. Binetti, B. Nacmias, S. Sorbi, R. Sanchez-Valle, A. Lladó, E. Gelpi, M.R. Almeida, I. Santana, J. Clarimon, A. Lleó, J. Fortea, A. de Mendonça, M. Martins, B. Borroni, A. Padovani, R. Matěj, Z. Rohan, A. Ruiz, G.B. Frisoni, G. M. Fabrizi, R. Vandenberghe, P.P. De Deyn, C. Van Broeckhoven, K. Sleegers, Genetic variability in SQSTM1 and risk of early-onset Alzheimer dementia: a European early-onset dementia consortium study, Neurobiol. Aging 36 (2015), 2005.e2015-2005.e2022.

[38] E. Teyssou, T. Takeda, V. Lebon, S. Boillée, B. Doukouré, G. Bataillon, V. Sazdovitch, C. Cazeneuve, V. Meininger, E. LeGuern, F. Salachas, D. Seilhean, S. Millecamps, Mutations in SQSTM1 encoding p62 in amyotrophic lateral sclerosis: genetics and neuropathology, Acta Neuropathol. 125 (2013) 511–522.

[39] J. van der Zee, T. Van Langenhove, G.G. Kovacs, L. Dillen, W. Deschamps, S. Engelborghs, R. Matěj, M. Vandenbulcke, A. Sieben, B. Dermaut, K. Smets, P. Van Damme, C. Merlin, A. Laureys, M. Van Den Broeck, M. Mattheijssens, K. Peeters, L. Benussi, G. Binetti, R. Ghidoni, B. Borroni, A. Padovani, S. Archetti, P. Pastor, C. Razquin, S. Ortega-Cubero, I. Hernández, M. Boada, A. Ruiz, A. de Mendonça, G. Miltenberger-Miltényi, F.S. do Couto, S. Sorbi, B. Nacmias, S. Bagnoli, C. Graff, H.-H. Chiang, H. Thonberg, R. Perneczky, J. Diehl-Schmid, P. Alexopoulos, G.B. Frisoni, C. Bonvicini, M. Synofzik, W. Maetzler, J.M. vom Hagen, L. Schöls, T.B. Haack, T.M. Strom, H. Prokisch, O. Dols-Icardo, J. Clarimón, A. Lleó, I. Santana, M.R. Almeida, B. Santiago, M.T. Heneka, F. Jessen, A. Ramirez, R. Sanchez-Valle, A. Llado, E. Gelpi, S. Sarafov, I. Tournev, A. Jordanova, E. Parobkova, G.M. Fabrizi, S. Testi, E. Salmon, T. Ströbel, P. Santens, W. Robberecht, P. De Jonghe, J.-J. Martin, P. Cras, R. Vandenberghe, P.P. De Deyn, M. Cruts, K. Sleegers, C. Van Broeckhoven, Rare mutations in SQSTM1 modify susceptibility to frontotemporal lobar degeneration, Acta Neuropathol. 128 (2014) 397–410.

[40] S. Ma, I.Y. Attarwala, X.-Q. Xie, SQSTM1/p62: a potential target for neurodegenerative disease, ACS Chem. Neurosci. 10 (2019) 2094–2114.

[41] Y. Duan, N. Kelley, Y. He, Role of the NLRP3 inflammasome in neurodegenerative diseases and therapeutic implications, Neural Regen. Res. 15 (2020) 1249–1250.

[42] M.E. Haque, M. Akther, M. Jakaria, I.S. Kim, S. Azam, D.K. Choi, Targeting the microglial NLRP3 inflammasome and its role in Parkinson's disease, Mov. Disord. : Off. J. Mov. Disorder Soc. 35 (2020) 20–33.

[43] E. Lee, I. Hwang, S. Park, S. Hong, B. Hwang, Y. Cho, J. Son, J.-W. Yu, MPTP-driven NLRP3 inflammasome activation in microglia plays a central role in dopaminergic neurodegeneration, Cell Death Differ. 26 (2019) 213–228.

[44] A. De Roeck, C. Van Broeckhoven, K. Sleegers, The role of ABCA7 in Alzheimer's disease: evidence from genomics, transcriptomics and methylomics, Acta Neuropathol. 138 (2019) 201–220.

[45] H. Li, T. Karl, B. Garner, Understanding the function of ABCA7 in Alzheimer's disease, Biochem. Soc. Trans. 43 (2015) 920–923.

[46] S.R. Yoshii, C. Kishi, N. Ishihara, N. Mizushima, Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane, J. Biol. Chem. 286 (2011) 19630–19640.

[47] C. Arkinson, H. Walden, Parkin function in Parkinson's disease, Science 360 (2018) 267–268.

[48] Alicia M. Pickrell, Richard J. Youle, The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease, Neuron 85 (2015) 257–273.

[49] T. Shen, J. Hu, Y. Jiang, S. Zhao, C. Lin, X. Yin, Y. Yan, J. Pu, H.-Y. Lai, B. Zhang, Early-onset Parkinson's disease caused by PLA2G6 compound heterozygous mutation, a case report and literature review, Front. Neurol. 10 (2019).

[50] O. Pansarasa, M. Bordoni, L. Diamanti, D. Sproviero, S. Gagliardi, C. Cereda, SOD1 in amyotrophic lateral sclerosis: "ambivalent" behavior connected to the disease, Int. J. Mol. Sci. 19 (2018) 1345.

[51] C. Li, W.-C. Xu, Z.-S. Xie, K. Pan, J. Hu, J. Chen, D.-W. Pang, F.-Q. Yang, Y. Liang, Cupric ions induce the oxidation and trigger the aggregation of human superoxide dismutase 1, PloS One 8 (2013), e65287.

[52] D.A. Bosco, G. Morfini, N.M. Karabacak, Y. Song, F. Gros-Louis, P. Pasinelli, H. Goolsby, B.A. Fontaine, N. Lemay, D. McKenna-Yasek, M.P. Frosch, J.N. Agar, J. P. Julien, S.T. Brady, R.H. Brown Jr., Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS, Nat. Neurosci. 13 (2010) 1396–1403.

[53] N. Fujiwara, M. Nakano, S. Kato, D. Yoshihara, T. Ookawara, H. Eguchi, N. Taniguchi, K. Suzuki, Oxidative modification to cysteine sulfonic acid of Cys111 in human copper-zinc superoxide dismutase, J. Biol. Chem. 282 (2007) 35933–35944.

[54] W.-C. Xu, J.-Z. Liang, C. Li, Z.-X. He, H.-Y. Yuan, B.-Y. Huang, X.-L. Liu, B. Tang, D.-W. Pang, H.-N. Du, Y. Yang, J. Chen, L. Wang, M. Zhang, Y. Liang, Pathological hydrogen peroxide triggers the fibrillization of wild-type SOD1 via sulfenic acid modification of Cys-111, Cell Death Dis. 9 (2018) 67.

[55] V.K. Mulligan, A. Kerman, R.C. Laister, P.R. Sharda, P.E. Arslan, A. Chakrabartty, Early steps in oxidation-induced SOD1 misfolding: implications for non-amyloid protein aggregation in familial ALS, J. Mol. Biol. 421 (2012) 631–652.
[56] M. Cozzolino, M.G. Pesaresi, I. Amori, C. Crosio, A. Ferri, M. Nencini, M.T. Carri, Oligomerization of mutant SOD1 in mitochondria of motoneuronal cells drives mitochondrial damage and cell toxicity, Antioxidants Redox Signal. 11 (2009) 1547–1558.
[57] M. Cozzolino, I. Amori, M.G. Pesaresi, A. Ferri, M. Nencini, M.T. Carri, Cysteine 111 affects aggregation and cytotoxicity of mutant Cu,Zn-superoxide dismutase associated with familial amyotrophic lateral sclerosis, J. Biol. Chem. 283 (2008) 866–874.
[58] A. Ferri, M. Cozzolino, C. Crosio, M. Nencini, A. Casciati, E.B. Gralla, G. Rotilio, J. S. Valentine, M.T. Carri, Familial ALS-superoxide dismutases associate with mitochondria and shift their redox potentials, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 13860–13865.
[59] J. Niwa, S. Yamada, S. Ishigaki, J. Sone, M. Takahashi, M. Katsuno, F. Tanaka, M. Doyu, G. Sobue, Disulfide bond mediates aggregation, toxicity, and ubiquitylation of familial amyotrophic lateral sclerosis-linked mutant SOD1, J. Biol. Chem. 282 (2007) 28087–28095.
[60] S. Nagano, Y. Takahashi, K. Yamamoto, H. Masutani, N. Fujiwara, M. Urushitani, T. Araki, A cysteine residue affects the conformational state and neuronal toxicity of mutant SOD1 in mice: relevance to the pathogenesis of ALS, Hum. Mol. Genet. 24 (2015) 3427–3439.
[61] E. Ratti, J.D. Berry, Chapter 42 - amyotrophic lateral sclerosis 1 and many diseases, in: T. Lehner, B.L. Miller, M.W. State (Eds.), Genomics, Circuits, and Pathways in Clinical Neuropsychiatry, Academic Press, San Diego, 2016, pp. 685–712.
[62] S. Hadano, S. Mitsui, L. Pan, A. Otomo, M. Kubo, K. Sato, S. Ono, W. Onodera, K. Abe, X. Chen, M. Koike, Y. Uchiyama, M. Aoki, E. Warabi, M. Yamamoto, T. Ishii, T. Yanagawa, H.-F. Shang, F. Yoshii, Functional links between SQSTM1 and ALS2 in the pathogenesis of ALS: cumulative impact on the protection against mutant SOD1-mediated motor dysfunction in mice, Hum. Mol. Genet. 25 (2016) 3321–3340.
[63] C.L. Bennett, S.G. Dastidar, S.-C. Ling, B. Malik, T. Ashe, M. Wadhwa, D.B. Miller, C. Lee, M.B. Mitchell, M.A. van Es, C. Grunseich, Y. Chen, B.L. Sopher, L. Greensmith, D.W. Cleveland, A.R. La Spada, Senataxin mutations elicit motor neuron degeneration phenotypes and yield TDP-43 mislocalization in ALS4 mice and human patients, Acta Neuropathol. 136 (2018) 425–443.
[64] M. Hirano, C.M. Quinzii, H. Mitsumoto, A.P. Hays, J.K. Roberts, P. Richard, L. P. Rowland, Senataxin mutations and amyotrophic lateral sclerosis, Amyotroph Lateral Scler. : Off. Publ. World Fed. Neurol. Res. Group on Motor Neuron Dis. 12 (2011) 223–227.
[65] F. Saudou, S. Humbert, The biology of huntingtin, Neuron 89 (2016) 910–926.
[66] M. Martinez-Vicente, Z. Talloczy, E. Wong, G. Tang, H. Koga, S. Kaushik, R. de Vries, E. Arias, S. Harris, D. Sulzer, A.M. Cuervo, Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease, Nat. Neurosci. 13 (2010) 567–576.
[67] R. Goold, M. Flower, D.H. Moss, C. Medway, A. Wood-Kaczmar, R. Andre, P. Farshim, G.P. Bates, P. Holmans, L. Jones, S.J. Tabrizi, FAN1 modifies Huntington's disease progression by stabilizing the expanded HTT CAG repeat, Hum. Mol. Genet. 28 (2018) 650–661.
[68] M. Kirschner, J. Gerhart, Evolvability, Proc. Natl. Acad. Sci. Unit. States Am. 95 (1998) 8420–8427.
[69] J.A. de Visser, J. Hermisson, G.P. Wagner, L. Ancel Meyers, H. Bagheri-Chaichian, J.L. Blanchard, L. Chao, J.M. Cheverud, S.F. Elena, W. Fontana, G. Gibson, T. F. Hansen, D. Krakauer, R.C. Lewontin, C. Ofria, S.H. Rice, G. von Dassow, A. Wagner, M.C. Whitlock, Perspective: evolution and detection of genetic robustness, Evol. Int. J. Org. Evol. 57 (2003) 1959–1972.
[70] H.-C. Yang, Y.-H. Wu, W.-C. Yen, H.-Y. Liu, T.-L. Hwang, A. Stern, D.T.-Y. Chiu, The redox role of G6PD in cell growth, Cell Death Canc. Cells 8 (2019) 1055.
[71] I. Hanukoglu, R. Rapoport, Routes and regulation of NADPH production in steroidogenic mitochondria, Endocr. Res. 21 (1995) 231–241.
[72] U. Raudvere, L. Kolberg, I. Kuzmin, T. Arak, P. Adler, H. Peterson, J. Vilo, g: Profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update), Nucleic Acids Res. 47 (2019) W191–W198.
[73] J.W. Harper, A. Ordureau, J.-M. Heo, Building and decoding ubiquitin chains for mitophagy, Nat. Rev. Mol. Cell Biol. 19 (2018) 93–108.
[74] W.J. Liang, Å.B. Gustafsson, The aging heart: mitophagy at the center of rejuvenation, Front. Cardiovasc. Med. 7 (2020).
[75] Y.-N. Rui, Z. Xu, B. Patel, A.M. Cuervo, S. Zhang, HTT/Huntingtin in selective autophagy and Huntington disease: a foe or a friend within? Autophagy 11 (2015) 858–860.
[76] N.D. Rudnick, C.J. Griffey, P. Guarnieri, V. Gerbino, X. Wang, J.A. Piersaint, J. C. Tapia, M.M. Rich, T. Maniatis, Distinct roles for motor neuron autophagy early and late in the $SOD1^{G93A}$ mouse model of ALS, Proc. Natl. Acad. Sci. Unit. States Am. 114 (2017) E8294–E8303.
[77] C. Yung, D. Sha, L. Li, L.S. Chin, Parkin protects against misfolded SOD1 toxicity by promoting its aggresome formation and autophagic clearance, Mol. Neurobiol. 53 (2016) 6270–6287.
[78] D.D. Martin, S. Ladha, D.E. Ehrnhoefer, M.R. Hayden, Autophagy in Huntington disease and huntingtin in autophagy, Trends Neurosci. 38 (2015) 26–35.
[79] B. Carroll, E.G. Otten, D. Manni, R. Stefanatos, F.M. Menzies, G.R. Smith, D. Jurk, N. Kenneth, S. Wilkinson, J.F. Passos, J. Attems, E.A. Veal, E. Teyssou, D. Seilhean, S. Millecamps, E.-L. Eskelinen, A.K. Bronowska, D.C. Rubinsztein, A. Sanz, V. I. Korolchuk, Oxidation of SQSTM1/p62 mediates the link between redox state and protein homeostasis, Nat. Commun. 9 (2018) 256.
[80] O. Pampliega, I. Orhon, B. Patel, S. Sridhar, A. Díaz-Carretero, I. Beau, P. Codogno, B.H. Satir, P. Satir, A.M. Cuervo, Functional interaction between autophagy and ciliogenesis, Nature 502 (2013) 194–200.
[81] M. Morleo, B. Franco, The autophagy-cilia Axis: an intricate relationship, Cells 8 (2019) 905.
[82] M. Alvarez-Satta, L. Moreno-Cugnon, A. Matheu, Primary cilium and brain aging: role in neural stem cells, neurodegenerative diseases and glioblastoma, Ageing Res. Rev. 52 (2019) 53–63.
[83] M. Kaliszewski, A.B. Knott, E. Bossy-Wetzel, Primary cilia and autophagic dysfunction in Huntington's disease, Cell Death Differ. 22 (2015) 1413–1424.
[84] E.C. Kennett, C.Y. Chuang, G. Degendorfer, J.M. Whitelock, M.J. Davies, Mechanisms and consequences of oxidative damage to extracellular matrix, Biochem. Soc. Trans. 39 (2011) 1279–1287.
[85] S. Dupre-Crochet, M. Erard, O. Nuβe, ROS production in phagocytes: why, when, and where? J. Leukoc. Biol. 94 (2013) 657–670.
[86] N.M. Shanbhag, M.D. Evans, W. Mao, A.L. Nana, W.W. Seeley, A. Adame, R. A. Rissman, E. Masliah, L. Mucke, Early neuronal accumulation of DNA double strand breaks in Alzheimer's disease, Acta Neuropathol. Commun. 7 (2019) 77.
[87] J.M. Carlson, J. Doyle, Complexity and robustness, Proc. Natl. Acad. Sci. Unit. States Am. 99 (2002) 2538–2545.
[88] M.J. Pinto, J.R. Pedro, R.O. Costa, R.D. Almeida, Visualizing K48 ubiquitination during presynaptic formation by ubiquitination-induced fluorescence complementation (UiFC), Front. Mol. Neurosci. 9 (2016) 43.
[89] J. Chakraborty, V. Basso, E. Ziviani, Post translational modification of Parkin, Biol. Direct 12 (2017) 6.
[90] D. Ding, X. Ao, Y. Liu, Y.-Y. Wang, H.-G. Fa, M.-Y. Wang, Y.-Q. He, J.-X. Wang, Post-translational modification of Parkin and its research progress in cancer, Canc. Commun. 39 (2019) 77.
[91] S. Bak, I.R. León, O.N. Jensen, K. Højlund, Tissue specific phosphorylation of mitochondrial proteins isolated from rat liver, heart muscle, and skeletal muscle, J. Proteome Res. 12 (2013) 4327–4339.
[92] S.F. Altschul, W. Gish, W. Miller, E.W. Myers, D.J. Lipman, Basic local alignment search tool, J. Mol. Biol. 215 (1990) 403–410.
[93] R.C. Edgar, MUSCLE: multiple sequence alignment with high accuracy and high throughput, Nucleic Acids Res. 32 (2004) 1792–1797.
[94] U. Raudvere, L. Kolberg, et al., g:Profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update), Nucleic Acids Res. 47 (W1) (2019 Jul 2) W191–W198, https://doi.org/10.1093/nar/gkz369.