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Review Article

Inborn errors of canonical autophagy in neurodegenerative diseases

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Abstract

Neurodegenerative disorders (NDDs), characterized by a progressive loss of neurons and cognitive function, are a severe burden to human health and mental fitness worldwide. A hallmark of NDDs such as Alzheimer's disease, Huntington's disease, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and prion diseases is disturbed cellular proteostasis, resulting in pathogenic deposition of aggregated protein species. Autophagy is a major cellular process maintaining proteostasis and integral to innate immune defenses that mediates lysosomal protein turnover. Defects in autophagy are thus frequently associated with NDDs. In this review, we discuss the interplay between NDDs associated proteins and autophagy and provide an overview over recent discoveries in inborn errors in canonical autophagy proteins that are associated with NDDs. While mutations in autophagy receptors seems to be associated mainly with the development of ALS, errors in mitophagy are mainly found to promote PD. Finally, we argue whether autophagy may impact progress and onset of the disease, as well as the potential of targeting autophagy as a therapeutic approach. Concludingly, understanding disorders due to inborn errors in autophagy—"autophagopathies"—will help to unravel underlying NDD pathomechanisms and provide unique insights into the neuroprotective role of autophagy, thus potentially paving the way for novel therapeutic interventions.

Keywords: autophagy; neurodegenerative diseases; innate immunity; monogenic diseases

Introduction

Neurodegenerative diseases as proteinopathies

Neurodegenerative diseases (NDDs) are a heterogenous group of neurological conditions characterized by a progressive loss of neurons [1–3]. This erosion of neuronal circuits eventually leads to a collapse of neurocognitive features including impaired motor function, cognitive decline, memory loss and behavioral alterations. Currently, more than 55 million people are affected by NDDs, with ageing as the greatest risk factor [4]. Considering the overall ageing population, the impact of NDDs on human health worldwide is expected to increase. Besides age, genetic factors are crucial contributors to the development and progression of NDDs. A hallmark of several prominent NDDs is the loss of proteostasis and pathological aggregation of cellular proteins [1]. These toxic aggregates often form insoluble amyloid fibers and are thought to be a key pathological mechanism. According to the aggregating protein, NDDs can also be classified into amyloidoses, tauopathies, α-synucleinopathies, TDP-43-associated proteinopathies and prion diseases (Fig. 1A).

Aggregated small **amyloid β (Aβ)** peptides are the major component of amyloid plaques in Alzheimer's disease (AD) [5]. They are derived from the amyloid-β precursor protein (APP) by cleavage during the amyloidogenic pathway by β-secretases and γ-secretases. Of note, while Aβ oligomers and deposits have been considered as the molecular driver of Alzheimer's pathogenesis and progression, therapeutic targeting of Aβ has repeatedly failed [6]. Filamentous lesions and deposits of fibrils of the microtubule-associated protein **tau** are defining features of AD and related tauopathies such as frontotemporal dementia (FTD) [7]. Aberrant hyperphosphorylation of tau in neurons leads to its aggregation into helical filaments. Notably, tauopathies are considered to be responsible for the majority of dementias [8]. **Alpha-synuclein (α-syn)** is a small 14 kDa cellular protein mainly expressed in the central and peripheral nervous system. While mainly α-helical in its non-pathogenic form, it transitions into a pathological β-sheet confirmation, that eventually aggregates to form amyloid-like fibrils accumulating in neurons in Lewy bodies in Parkinson's disease (PD) or dementia with Lewy bodies (LBD) [9]. In multiple system atrophy (MSA) α-syn aggregates form mainly in glia cells [9]. α-syn aggregation/co-aggregation is observed in ~30%–50% of AD cases [10–12]. Mutated **Huntingtin (Htt)** with a polymorphic locus containing more than 36 CAG codons (coding glutamine, Q) is thought to be the main molecular cause of Huntington's disease (HD). The number of CAG repeats directly correlated with the onset and severity of the disease. Polyglutamine (polyQ) expanded Htt forms amyloid-like protein aggregates [13] which may be part of the HD pathogenesis. **TAR DNA-binding protein 43**

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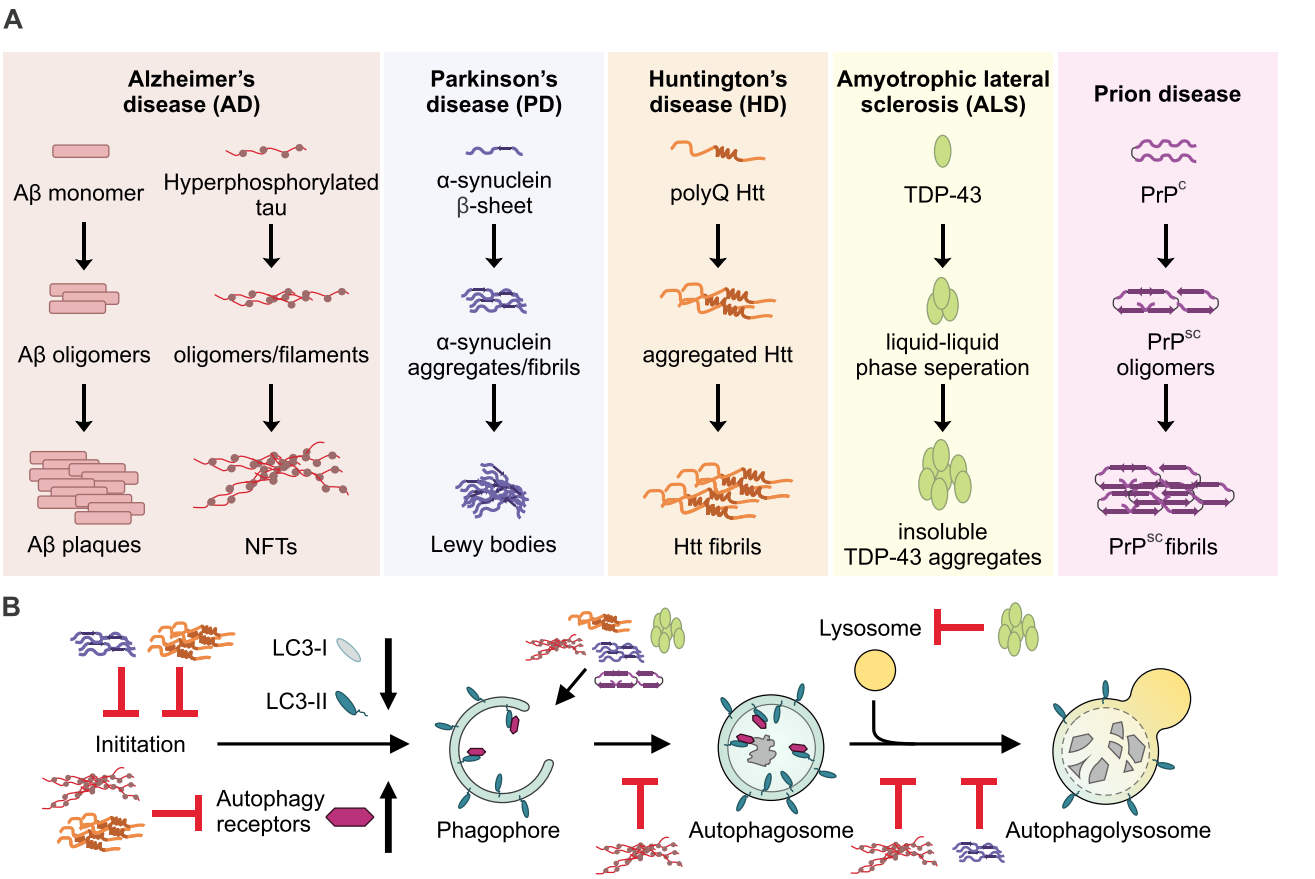

Figure 1. The interplay between autophagy and NDDs. (A) Aβ and hyperphosphorylated tau protein, β-sheet α-synuclein, Polyglutamine (polyQ) huntingtin (Htt), neurofibrillary tangles (NFTs), TDP-43 and misfolded prion protein (PrP^{Sc}) are aggregated proteins found in proteinopathies. Alzheimer's disease (AD), column 1 (red); Parkinson's disease (PD), column 2 (blue); Huntington's disease (HD), colum 3 (orange); amyotrophic lateral sclerosis (ALS), column 4 (green); prion disease, column 5 (purple). (B) Proteins (aggregates) associated with NDDs interact with the autophagic pathway at multiple levels. Autophagy initiation is inhibited by Htt fibrils and α-synuclein fibrils. After LC3B-I to LC3B-II conversion, cargo like misfolded/aggregated NDD associated proteins are recruited to the budding phagophore by specific autophagy receptors. In turn autophagy receptor function is disturbed by Htt fibrils and NFTs. To degrade the cargo, the closed autophagosome fuses with a lysosome to form an autophagolysosome. Insoluble TDP-43 interferes with lysosome function, whereas NFTs and α-synuclein fibrils perturb autophagosome to autophagolysosome transition.

(TDP-43) is a highly conserved nucleic acid binding protein and its aggregation is a common feature of several NDDs including amyotrophic lateral sclerosis (ALS), FTD and AD [14]. TDP-43 pathology is most prominent in ALS, with more than 90% of the cases exhibiting cytoplasmic aggregates that spread in characteristic stages [15]. Misfolding of cellular **Prion protein (PrP^C)** into β-sheet rich, aggregation-prone infectious **PrP^{Sc}** is the underlying cause of fatal Prion diseases or "transmissible spongiform encephalopathies" among them Creutzfeld-Jacob disease [16]. As opposed to other proteinopathies, prion protein aggregates have been shown to transmit the disease [17].

Taken together, it is conceivable that disturbance of proteostasis governs the onset and/or promotes progression of proteinopathic NDDs. The core of proteostasis maintenance in cells are chaperones that reduce misfolding, catabolic systems that degrade misfolded proteins such as the ubiquitin-proteasome system (UPS), and autophagy [18].

Autophagy maintains proteostasis

Macroautophagy (hereafter referred to as autophagy) is an evolutionary ancient catabolic pathway that is active in virtually every cell [19]. It is essential to maintain cellular proteostasis and an important part of innate immunity, providing defenses against pathogens. In a nutshell, autophagy facilitates (targeted) lysosome-associated degradation of obsolete/damaged organelles (e.g. degradation of mitochondria in mitophagy) and cellular or pathogen-associated proteins [20, 21]. Initiation is guided by the activity of kinases. *AMP-activated protein kinase* (AMPK1) promotes, whereas mammalian target of rapamycin (mTOR) and Casein kinase 2 (CSNK2) oppose autophagy activation [21–23]. Initiation converges in the activation of the Unc-51-like autophagy-activating kinases 1 (ULK1) complex that promotes the formation of a double-membranous structure called the phagophore [24]. The membranes are recruited by autophagy-related protein 9 (ATG9) in a Vacuolar protein sorting ortholog 35 (Vps35)-dependent manner [25, 26]. The budding autophagic vesicle (=autophagosome) is decorated with lipidated-ATG8 like proteins such as LC3B-II, promoting elongation of the autophagosome and the engulfment of cytoplasmic cargo. In selective autophagy, highly specific autophagy receptors recruit cargo earmarked by ubiquitin, among them Sequestosome-1 (SQSTM1/p62), Calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2/NDP52) or optineurin (OPTN) [27]. A master regulator of autophagy receptor phosphorylation and activation is Tank-binding kinase 1 (TBK1) [28, 29]. During mitophagy, obsolete mitochondria are recognized by PTEN-induced kinase 1 (PINK1), which causes activation of the E3 ligase parkin, that decorates the outer mitochondrial membrane with ubiquitin, which is in turn

recognized by OPTN [30]. Finally, the autophagosome matures and fuses with a lysosome to form the autophagolysosome followed by degradation of the inner membrane and the cargo by acidic hydrolases [31].

Main text

The interplay between autophagy and NDD-associated proteins

The majority of NDD-associated proteins were shown to be targeted by autophagy [32] (Fig. 1B). Aβ, insoluble tau and mouse Htt were shown to be cleared by activation of autophagy dependent on p62 [33–36]. Conversely, autophagy-deficient mice show increased extracellular Aβ deposition and intracellular Aβ accumulation [37–39], while lack of autophagy in microglia aggravates tau pathology [40]. Pharmacological activation of autophagy mitigates cognitive defects of AD model mice [38]. Curiously, it was also reported that autophagy may promote extracellular Aβ secretion and deposition [41] and the autophagy adaptor TRIAD3A was suggested to promote tau fibrillation [42], suggesting a more complex role of autophagy in AD. Inhibition of autophagy attenuated the clearance of Htt aggregates both in cell culture and rats [35, 43–45]. α-syn is targeted for degradation by both autophagy and the proteasome [46, 47]. TDP-43 pathology was reduced in an ALS mouse model by autophagy induction [48, 49] and TDP-43 aggregates were found in autophagosomes [50]. Of note, TDP-43 secretion may be promoted by autophagy-associated processes [51]. The impact of autophagy on prion diseases is less well explored, however, older studies suggest that protease resistant prion may be targeted by autophagy [52] and induction of autophagy counteracts prion mediated neurotoxicity [53, 54].

In turn, NDD-associated protein aggregates impact autophagy. Aβ fibrils reduce autophagic flux in AD models and AD patients [55–57] which may additionally fuel deposition of fibrils [58]. Similarly, tau accumulation inhibits autophagy via impairing ESCRT-III complex formation [59] and disturbance of the autophagosomal-lysosomal axis is associated with tauopathies [60]. Prolonged polyQ tracts in Htt outcompete binding of ataxin-3 to beclin-1, leading to beclin-1 degradation and inhibition of autophagy initiation [61]. Of note, tau as well as Htt fibrils escape clearance by autophagy by stealthing in p62 coats [62, 63]. α-syn impacts autophagy by impairing SNAP29-mediated autophagosome-lysosome fusion [64]. Pathogenic, mutated α-syn (A53T) is able to bind to tuberous sclerosis protein (TSC) 2, which destabilizes the TSC1-TSC2 complex, eventually leading to aberrant mTOR activity [65]. Of note, soluble α-syn (*SNCA*x3) impairs autophagy/mitophagy [66] and may disturb autophagy by accumulation at the ER, eventually leading to the aggregation of immature β-glucocerebrosidase (GCase) [67]. TDP-43 was shown to impair autophagosome turnover by increasing TFEB activity [68] and interfering with lysosomal function thus presumably preventing its own degradation [69]. The prion protein was also suggested to play a role in autophagy [70], and human prion-induced autophagy flux was reported to contribute to primary neuron cell damage [71].

Improving our understanding of the intricate relationship between autophagy and NDDs may open up new avenues for both molecular insights and therapeutic interventions.

Patient variants in autophagy genes linked to NDDs

In the recent years, monogenic variants of core autophagy proteins have been causally linked to the development of neurodegenerative pathology providing genetic evidence for the importance of autophagy and may help to unravel the complex pathomechanisms [72]. Here we focused on recently discovered mutations in core autophagy proteins associated with five major NDDs: AD, PD, HD, ALS and Prion diseases (Fig. 2, overview in [73]).

Alzheimer's disease (AD) is a form of dementia mainly characterized by symptoms like memory loss and cognitive dysfunction [74] linked to hyperphosphorylated tau proteins, that aggregates to neurofibrillary tangles [7], and Aβ aggregates derived from APP cleavage [5]. Although more than 90% of AD cases are sporadic, AD was associated with mutations in presenilin-1 and -2 (PSEN1; PSEN2) and Sortilin Related Receptor 1 (SORL1) [75, 76]. Recently, AD-associated variant p.N299S in acetyl-Coenzyme A acyltransferase 1 (ACAA1) was described to eventually lead to impaired autophagosome-lysosome fusion and function [77]. In all cases autophagy was disturbed, however, the mutations did not affect core autophagy genes.

Parkinson's disease (PD) is associated with accumulation and aggregation of α-syn within dopaminergic neurons. Although mainly sporadic (85%–90%) patient-associated variants are frequently found in genes involved in mitophagy (Fig. 2), usually in the E3 ligases parkin and PINK1. Of note, PINK1 mutations are especially common in early onset PD [78–80]. However, it should be noted that many mutations in *PARKIN*, may lead to a disturbance of α-syn proteasomal degradation and may not affect mitophagy. Variants of parkin include more than 10 likely pathogenic missense mutations (Table 1 and [120]), often resulting in dysfunctional gene expression. More recently, analyses of cells from a PD patient with mutated *PARKIN* (B125: homozygous c.1072Tdel) revealed a destabilization of active Rab7, leading to decreased mitochondria-lysosome contact, and thus amino acid accumulation in lysosomes [118]. Systematic analyses of PINK1 mutations associated with PD showed that more than 16 missense variants could be considered pathogenic [129]. Most recently, further putatively pathogenic variants were discovered, including p.F385S [130]. Mutated VPS35 p.D620N associated with PD patients, was shown to impair mitophagy and autophagy [123]. In addition, VPS35 p.D620N disturbed Rab9 dependent non-canonical autophagy [131]. PD associated mutations in the lysosomal GBA (p.N370S, p.L444P) lead to lysosomal dysfunction, inhibiting chaperone mediated autophagy, however simultaneously maintaining normal autophagy levels via increase in ULK1 phosphorylation, highlighting a possible compensatory mechanism [124].

Huntington's disease (HD) is defined by the aberrant presence of CAG repeat expansions in the Htt gene, resulting in the expression of Htt with expanded polyQ tracts at the C-terminus. These variants are prone to aggregation, formation of amyloid-like fibrils as well as neurofibrillary tangles [13]. Of note, the risk variant p.V471A in the core autophagy gene *ATG7* is associated with early onset of HD, suggesting that functional autophagy may clear pathological aggregation [126, 127]. Recently it was shown that the expression of the miRNA miR-29b-3p targeting STAT3 and ultimately reducing autophagy, increases with age potentially increasing HD symptom severity [132].

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive loss of upper and lower motoneurons, leading to death within 3–5 years after symptoms onset [15]. Even though the associated risk genes are functionally heterogeneous, intracellular TDP-43 aggregates characterize up to 97% of the cases [133]. Of note, as a large number of mutations in core autophagy genes were identified as risks in the past years (Table 1, Fig. 2), we discuss here the most recent findings. For example,

Table 1. Variants of core autophagy genes, mechanism and associated diseases.

Disease	Genes	Mutation	Identified in	Mechanism
ALS	*SQSTM1*	p.L341V	[81]	Reduced binding affinity to ubiquitin [82] Reduction in binding affinity to hATG8 [83]
		p.P392L		Reduced binding affinity to ubiquitin [82]
		p.G425R		Loss of binding to ubiquitin [82]
		p.A16V p.D80E p.E81K p.V90M p.I99L p.R107W p.R212C p.G219V p.S226P p.P232T p.N239K p.D258N p.E280* p.G297S p.R312H p.A33V p.V153I p.P228L p.V234V p.H261H p.S318P		NA
		p.R110C		Reduced phosphorylation of Ser-403 and Ser-349 [84] necessary for SQSTM1/KEAP1 interaction, also reducing NRF2 activity (Oxidative Stress response)
		p.D129N		Reduce affinity towards N-degron [85]
		p.K238del	[86]	Loss of function, reduced mitochondrial respiration, increased cytosolic ROS production, reduced complex 1 activity of the electron transport chain and lowered mitochondrial membrane potential [87]
		p.R321C		Increased levels of p62 and LC3B suggesting autophagy blockage [88]
		p.G411S		Loss of mono- and polyubiquitin-binding [89]
		p.A53T p.M87V p.E155K p.K238E p.E274D p.P296P p.S318S p.V346V p.A390* p.P438L p.P439L p.V346V p.S370P	[90]	NA
		p.K102E		Impaired formation of disulphide-linked conjugates upon oxidative stress and thus induction of autophagy [91]
		p.P348L		Reduced Keap1 binding [92]
	OPTN	p.E478G	[93]	Inhibits autophagosome maturation [94] Impaired mitophagy [95]
		p.G23* p.Q165* p.S262* p.L568L		NA
		p.Q398*		Loss of ubiquitin binding [96]
		p.L430Rfs*16 p.K440Nfs*8 p.D220Mfs*12		NA
		p.148_184del-, Ex5del		NA
		p.H3Y p.P16A p.K59N p.A93P p.R96L		NA

(continued)

Table 1. Continued.

Disease	Gene	Mutations	Identified in	Mechanism
		p.D127R p.A136V p.V161M p.R271C p.T282P p.V295F p.Q314L p.E322K p.K395R p.M447R p.I451T p.M468R p.A481V p.K489E p.L494W p.L500P p.E516Q p.R545Q p.K557T p.Q564H		
		p.Q454E		Dysregulation of NF-kB and mitophagy [97]
	TBK1	p.E696K	[98]	Impairing lysosomal degradation, Rab7 phosphorylation, OPTN binding, and mitophagy [30, 99–102]
		p.R573G		Reduction in kinase activity [103]
		p.I43V p.L62P p.L94S∗ p.D118N p.G121D∗ p.R143C∗ p.R229S p.G244V p.I246T p.R271L∗ p.K291E p.G294D p.L306I∗ p.H322Y p.I334T p.R384W∗ p.I397T p.K401E p.I418V p.I475T∗ p.E476K∗ p.I515T p.A535T p.K570R		NA
		p.T320Qfs∗40 p.I450Kfs∗15 p.V479Gfs∗4 p.Y185∗ p.T77Wfs∗4 p.A417∗ 690-713del p.R440∗		Loss of function [104]
		p.R47H		loss of kinase activity and loss of IRF3 activation [105]
		p.R357Q		abolish OPTN binding and phosphorylation, failure to oligomerize and reduced steady-state-level [105]
		p.M559R p.G217R		loss of kinase activity and dimerization, loss of OPTN binding [99, 104, 105]
		p.I305T p.A571V p.M598V		NA

(continued)

Table 1. Continued.

Disease	Genes	Mutations	Identified in	Mechanism
		p.Y105C p.R308Q	[106]	Impaired interaction with OPTN and reduced p62 phosphorylation [105]
		p.M623fs p.Q629fs p.T31A p.R358H		NA
		p.E643del		NA
		p.Q2del p.R117del p.R357del p.R440del p.R444del p.S499del	[107]	NA
		p.L10S p.S151F p.I257T p.L277V p.T331I p.T343S p.R440Q p.C471Y p.I522M p.R573H p.Q580H p.I710N		NA
		p.N22H p.S151C		Reduced p62 S403 phosphorylation [105]
		p.R25H p.R47H p.R134H p.R228H p.V132E p.N129D		Reduced kinase activity/loss of function [105]
		p.R228H		Reduced autophosphorylation/partial loss of function [108]
		p.Q565P		Reduced phosphorylation of p62 [105]
		p.Y394D		Early onset of the disease/mechanism not known yet [107]
	CCNF	p.S621G	[109]	Inhibits p62 foci formation [109]
	UBQLN2	p.P497H p.P509S	[110]	Reduced mitophagy [110]
	C9ORF72	G4C2 repeats		Impaired autophagic flux, autophagosome biogenesis, and fusion with lysosomes. Perturbed lysosome metabolism (axonal transport, maturation (enlarged and reduced numbers)) Increased phosphorylated TBK1 (S172) levels [111–113]
	PFN1	p.C71G p.M114T	[114]	Impaired endolysosomale processing [114]
PD	*PINK1*	p.K219A p.G309D p.L347P p.D362A p.D384A p.G386A p.G409V p.E417G	[115]	Reduced kinase activity [115]
		p.Q456*	[116]	No kinase activity [116]
		p.V170G	[117]	Reduced activity/partial loss of function [117]
	PRKN	p.C431S	[118]	Decrease in mitochondria lysosome contact [118]
		p.Q34Rfs*5 p.Q34Rfs*10 p.V3Efs*3 p.A138Gfs*7 p.N52Mfs*29 p.G34Rfs*5 p.P113Tfs*51 p.D18Vfs*26 p.R156Sfs*29	mdsgene.org	NA

(continued)

Table 1. Continued.

Disease	Genes	Mutations	Identified in	Mechanism
		p.W445* p.C446F p.Q311*		NA
		p.R275W		Reduced PRKN translocation/loss of function [119]
		p.C212Y p.C253Y		Reduced protein stability/loss of function [120]
		p.T240M p.T240R		Residue necessary for E2-binding/likely loss of function [121]
		p.G430D		Residue necessary for RING2 domain function/likely loss of function [121]
		p.R42P p.V56E		Reduced protein stability/likely loss of function [121]
		p.T415N		Loss of function [122]
		p.W453*		Loss of substrate ubiquitination [121]
	VPS35	p.D620N	[123]	Impaired auto- and mitophagy [123]
	GBA	p.N370S p.L444P	[124]	Lysosomal dysfunction [124]
		p.E326K	[125]	Reduced TFEB activity, increase in p-RPS6 levels and decrease in DEPTOR [125]
HD	*ATG7*	p.V471A	[126]	Loss of function [126–128]
AD	*ACAA1*	p.N299S	[77]	Impaired lysosome function and lysosome-autophagosome fusion [77]

several mutations (p.L341V, p.P392L, p.G425R) in one of the major cargo-recruitment receptors of autophagy, SQSTM1/p62 were shown to result in reduced binding affinity to ubiquitin, eventually leading to reduced lysophagy [82]. p.L341V in p62 lowers the binding affinity to certain hATG8 proteins [83]. (Table 1). A patient-associated variant of the autophagy receptor OPTN (p.E478G) has been shown to interfere with the maturation of autophagosomes and MYO6 recruitment, inhibiting autophagic flux [94]. This variant negatively influences OPTN and UBQLN2 recycling at endosomes [134]. Mutations in TBK1, a central regulatory kinase of autophagy, have been frequently linked to impaired autophagy and increased neuroinflammation in ALS [135]. So far more than 90 mutations in TBK1 were associated with ALS [99]. Most of the TBK1 related mutations are deleterious and most likely lead to haploinsufficiency [99, 104] (Table 1). Lower TBK1 levels prevent efficient maturation of autophagosomes due to reduced phosphorylation of autophagy receptors [136]. Many missense mutations in TBK1 show a loss of function phenotype, however the exact mechanism for all mutations is currently not known [104] (Table 1, and [104, 137]). More recently it was reported that TBK1 p.E696K lowers its expression levels, impairs lysosomal degradation, and elevates Rab7 phosphorylation levels [100]. Of note, hyperactive Rab7 leads in turn to mTORC1 activation, further inhibiting autophagy [101]. In addition, TBK1 p.E696K has been shown to reduce binding affinity towards OPTN [99]. Another group reported that the TBK1 p.R573G mutation leads to a reduced kinase activity, yet autophagic flux levels were not altered [103]. In addition to core autophagy proteins, genetic mutations in other autophagy regulating factors were recently identified as risks genes in ALS. For example, CCNF (p.S621G) reduces p62 foci formation [109] and mutated UBQLN2 (p.P497H, p.P509S) decreases mitophagy [110]. G4C2 repeats in C9ORF72 were suggested to reduce biogenesis of autophagosomes and autophagosome-lysosome fusion [111–113]. Longer repeats cause sequestration of TBK1 into inclusion bodies, thus reducing TBK1 activity [138]. Mutant profilin 1 (PFN1) (p.C71G, p.M114T) negatively impacts endo-lysosomal processing [114].

Transmissible spongiform encephalopathies (TSE), or prion diseases, are characterized by aggregates of misfolded Prion protein, PrP^{sc} [16]. TSEs are unique among NDDs as epidemiological evidence supports that they are transmitted between people, similar to infectious agents [17]. While the last decades have elucidated numerous pathogenic variants of the *PRNP* gene, up to date, there are no mutations in autophagy related genes described which are associated with prion diseases.

Concluding remarks

Molecular analysis of human genetic variants gave unique insights into the pathophysiological mechanisms of autophagy in NDDs. Patient-associated mutations have established a clear genetic link between autophagy and selected NDDs. For example, there is a clear association between PD and perturbed mitophagy. The most studied mitophagy pathway is dependent on two proteins central for familiar PD, PINK1 and parkin [80, 120]. Mutations in these two proteins, which often lead to dysfunctional mitophagy are considered to be the most common genetic link to PD. Curiously, ALS seems to be predominantly associated with variants of autophagy receptors such as p62 or OPTN, or variants of autophagy-receptor activating kinases such as TBK1 [29, 134, 137]. That said, different stages/pathways of autophagy are clearly associated to specific NDDs. While the molecular details of mitophagy in PD has been extensively analyzed [9, 30, 66, 79, 118], the notable concentration of ALS-associated autophagy receptor mutations needs to be further explored. Other NDDs such as AD, HD or prion diseases were shown to impact and be impacted by autophagy, but prominent mutations in core autophagy proteins were not (yet) associated. Finally, a large number of patients develop NDDs sporadically, especially AD or PD, and no clear genetic condition could be associated. Of note, the age of onset of sporadic NDDs is usually late in life. It is tempting to speculate that waning efficiency of autophagy due to ageing may increase the chances of sporadic formation of toxic protein aggregates.

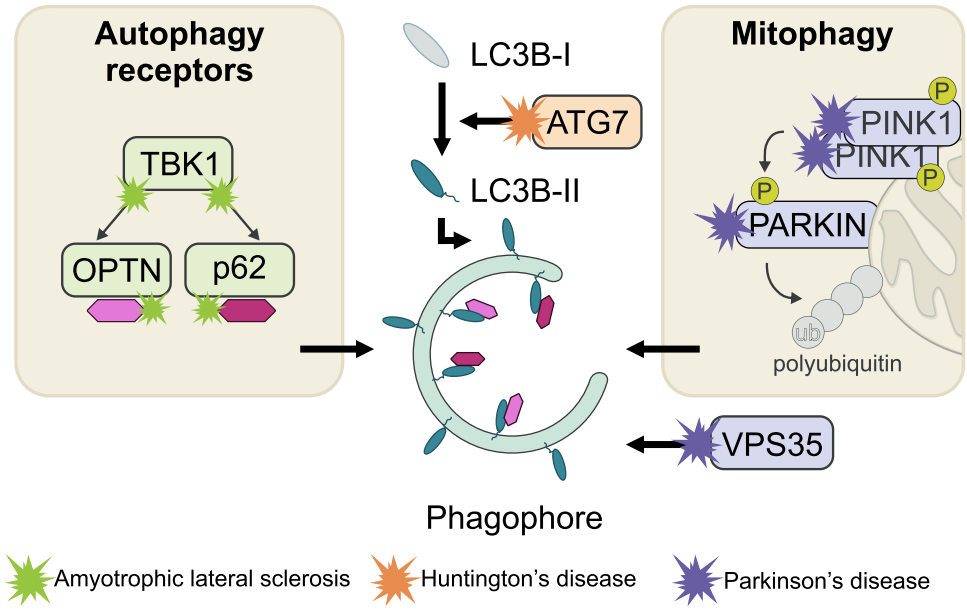

Figure 2. Mutations in autophagy initiation associated genes in NDDs. TBK1 activates autophagy receptors such as OPTN and p62 by phosphorylation, which in turn recruit cargo to the budding phagophore. Conversion of LC3B-I to membrane-associated LC3B-II is facilitated by ATG7 and required for autophagosome elongation and closure. Phagophore formation is promoted by membrane recruitment via VPS35. During mitophagy, damaged or obsolete mitochondria are recognized by PINK1, which in turn activates the E3 ubiquitin ligase parkin. Parkin catalyzes the ubiquitination of the mitochondrial outer membrane. The earmarked mitochondria are then recruited to autophagosomes by OPTN. NDD associated mutations that impair function in autophagy are highlighted in respective color.

However, the role of age-impaired autophagy in the development and progression of NDDs needs to be analyzed.

NDD-associated defects in genes related to autophagy may not automatically show involvement of canonical autophagy. For example, non-canonical autophagy such as LC3-associated phagocytosis [139] was shown to facilitate AD in mouse models [39]. In addition, many autophagy proteins play secondary roles in secretory processes [140], which can impact cytokine secretion during neuroinflammation [141] or direct secretion of fibrils [41, 51]. While canonical autophagy is considered to solely lead to the degradation of intracellular proteins/aggregates, autophagy-like processes may also target extracellular NDD-associated proteins and aggregates. It is thus crucial for future studies to delineate the exact role and impact of NDD associated gene variants in autophagy, autophagy-like processes or even non-autophagy-related processes.

Emerging evidence suggests that autophagy is a cellular defense mechanism against NDDs, preventing detrimental oligomer formation, or even clearing aggregates [142, 143]. Convincing preclinical data highlighting the therapeutic potential of autophagy modulation is currently accumulating [142, 144]. For example, activation of autophagy by the mTOR inhibitor Temsirolimus decreased Htt aggregates in mouse studies [145]. Similarly, targeting mTOR was shown to reduce progression of AD in models [146–148]. Along these lines, modulation of the activity of kinases involved in the activation of autophagy such as AMPK were also shown to decrease aggregate formation in cellular and mouse models of AD, PD, and HD. In HD, therapeutic strategies based on targeting mitophagy, such as ROCK inhibitors [149, 150], were tested in proof-of-principle experiments. Unfortunately, despite ongoing clinical trials, there are currently no approved therapeutic interventions based on autophagy modulation. The reasons are likely multifactorial, and include strong side-effects, little autophagy-specificity and difficult central nervous system delivery of currently available compounds.

Despite rapid progress in the identification of NDD-associated mutations in recent years, the underlying molecular mechanism(s) and how do they contribute to the onset and progression of the disease often remain understudied. Importantly, it also needs to be addressed, why do certain mutations lead to a specific type of NDD. In addition, insights from understanding the molecular basis of mendelian NDD-associated autophagopathies will improve our understanding of the protective role of autophagy, and help unravel the molecular biology of NDD onset and progression. Most importantly, inspired by our understanding of the molecular details the way for direly needed novel therapeutic interventions in NDDs is paved.

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References

1. Wilson DM, Cookson MR, Bosch LVD. *et al.* Hallmarks of neurodegenerative diseases. *Cell* 2023;**186**:693–714.
2. Erkkinen MG, Kim M-O, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harb Perspect Biol* 2018;**10**:a033118.
3. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. *Cold Spring Harb Perspect Biol* 2017;**9**:a028035.
4. Hou Y, Dan X, Babbar M. *et al.* Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* 2019;**15**:565–581.
5. Chen G, Xu T, Yan Y. *et al.* Amyloid beta: structure, biology and structure-based therapeutic development. *Acta Pharmacol Sin* 2017;**38**:1205–1235.
6. Zhang Y, Chen H, Li R. *et al.* Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. *Sig Transduct Target Ther* 2023;**8**:1–26.
7. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. *Annu Rev Neurosci* 2001;**24**:1121–1159.
8. Devi G. Chapter 12—the tauopathies. In: Younger D.S. (ed.), *Handbook of Clinical Neurology, Motor System Disorders, Part II: Spinal Cord, Neurodegenerative, and Cerebral Disorders and Treatment*, Vol. **196**. Amsterdam, Netherlands: Elsevier, 2023, 251–265.
9. Calabresi P, Mechelli A, Natale G. *et al.* Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. *Cell Death Dis* 2023;**14**:1–16.
10. Shim KH, Kang MJ, Youn YC. *et al.* Alpha-synuclein: a pathological factor with Aβ and tau and biomarker in Alzheimer's disease. *Alzheimers Res Ther* 2022;**14**:201.
11. van der Gaag BL, Deshayes NAC, Breve JJP. *et al.* Distinct tau and alpha-synuclein molecular signatures in Alzheimer's disease with and without Lewy bodies and Parkinson's disease with dementia. *Acta Neuropathol* 2024;**147**:14.
12. Bellomo G, Toja A, Paolini Paoletti F. *et al.* Investigating alpha-synuclein co-pathology in Alzheimer's disease by means of cerebrospinal fluid alpha-synuclein seed amplification assay. *Alzheimers Dement* 2024;**20**:2444–2452.
13. DiFiglia M, Sapp E, Chase KO. *et al.* Aggregation of huntingtin in neuronal Intranuclear inclusions and dystrophic neurites in brain. *Science* 1997;**277**:1990–1993.
14. Jo M, Lee S, Jeon Y-M. *et al.* The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies. *Exp Mol Med* 2020;**52**:1652–1662.
15. Braak H, Brettschneider J, Ludolph AC. *et al.* Amyotrophic lateral sclerosis–a model of corticofugal axonal spread. *Nat Rev Neurol* 2013;**9**:708–714.
16. Scheckel C, Aguzzi A. Prions, prionoids and protein misfolding disorders. *Nat Rev Genet* 2018;**19**:405–418.
17. Weissmann C, Enari M, Klöhn P-C. *et al.* Transmission of prions. *Proc Natl Acad Sci* 2002;**99**:16378–16383.
18. Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing. *Nat Rev Mol Cell Biol* 2019;**20**:421–435.
19. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. *Nature* 2011;**469**:323–335.
20. Klute S, Sparrer KMJ. Friends and foes: the ambivalent role of autophagy in HIV-1 infection. *Viruses* 2024;**16**:500.
21. Feng Y, He D, Yao Z. *et al.* The machinery of macroautophagy. *Cell Res* 2014;**24**:24–41.
22. Hoenigsperger H, Koepke L, Acharya D. *et al.* CSNK2 suppresses autophagy by activating FLN-NHL-containing TRIM proteins. *Autophagy* 2024;**20**:994–1014.
23. Kim J, Kundu M, Viollet B. *et al.* AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 2011;**13**:132–141.
24. Hurley JH, Young LN. Mechanisms of autophagy initiation. *Annu Rev Biochem* 2017;**86**:225–244.
25. Mailler E, Guardia CM, Bai X. *et al.* The autophagy protein ATG9A enables lipid mobilization from lipid droplets. *Nat Commun* 2021;**12**:6750.
26. Zavodszky E, Seaman MNJ, Moreau K. *et al.* Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. *Nat Commun* 2014;**5**:3828.
27. Gubas A, Dikic I. A guide to the regulation of selective autophagy receptors. *FEBS J* 2022;**289**:75–89.
28. Thurston TLM, Ryzhakov G, Bloor S. *et al.* The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nat Immunol* 2009;**10**:1215–1221.
29. Sparrer KMJ, Gableske S, Zurenski MA. *et al.* TRIM23 mediates virus-induced autophagy via activation of TBK1. *Nat Microbiol* 2017;**2**:1543–1557.
30. Adriaenssens E, Nguyen TN, Sawa-Makarska J. *et al.* Control of mitophagy initiation and progression by the TBK1 adaptors NAP1 and SINTBAD. *Nat Struct Mol Biol* 2024;**31**:1717–1731.
31. Yim WW-Y, Mizushima N. Lysosome biology in autophagy. *Cell Discov* 2020;**6**:6.
32. Park H, Kang J-H, Lee S. Autophagy in neurodegenerative diseases: a hunter for aggregates. *Int J Mol Sci* 2020;**21**:3369.
33. Fu Y, Wu P, Pan Y. *et al.* A toxic mutant huntingtin species is resistant to selective autophagy. *Nat Chem Biol* 2017;**13**:1152–1154.
34. Spilman P, Podlutskaya N, Hart MJ. *et al.* Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-β levels in a mouse model of Alzheimer's disease. *PLoS One* 2010;**5**:e9979.
35. Ravikumar B, Duden R, Rubinsztein DC. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. *Hum Mol Genet* 2002;**11**:1107–1117.
36. Berger Z, Ravikumar B, Menzies FM. *et al.* Rapamycin alleviates toxicity of different aggregate-prone proteins. *Hum Mol Genet* 2006;**15**:433–442.
37. Carosi JM, Hein LK, van den Hurk M. *et al.* Retromer regulates the lysosomal clearance of MAPT/tau. *Autophagy* 2021;**17**:2217–2237.
38. Wu S, Wei Y, Li J. *et al.* SIRT5 represses neurotrophic pathways and Aβ production in Alzheimer's disease by targeting autophagy. *ACS Chem Neurosci* 2021;**12**:4428–4437.
39. Heckmann BL, Teubner BJW, Tummers B. *et al.* LC3-associated endocytosis facilitates β-amyloid clearance and mitigates neurodegeneration in murine Alzheimer's disease. *Cell* 2019;**178**:536–551.e14.
40. Xu Y, Propson NE, Du S. *et al.* Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. *Proc Natl Acad Sci* 2021;**118**:e2023418118.
41. Nilsson P, Loganathan K, Sekiguchi M. *et al.* Aβ secretion and plaque formation depend on autophagy. *Cell Rep* 2013;**5**:61–69.
42. Zhou J, 'an Chuang Y, Redding-Ochoa J. *et al.* The autophagy adaptor TRIAD3A promotes tau fibrillation by nested phase separation. *Nat Cell Biol* 2024;**26**:1274–1286.
43. Tsvetkov AS, Arrasate M, Barmada S. *et al.* Proteostasis of polyglutamine varies among neurons and predicts neurodegeneration. *Nat Chem Biol* 2013;**9**:586–592.
44. Krüger U, Wang Y, Kumar S. *et al.* Autophagic degradation of tau in primary neurons and its enhancement by trehalose. *Neurobiol Aging* 2012;**33**:2291–2305.

45. Wei Y, Zhou J, Wu J. *et al.* ERβ promotes Aβ degradation via the modulation of autophagy. *Cell Death Dis* 2019;**10**:1–13.
46. Webb JL, Ravikumar B, Atkins J. *et al.* α-Synuclein is degraded by both autophagy and the proteasome∗. *J Biol Chem* 2003;**278**: 25009–25013.
47. Choi I, Zhang Y, Seegobin SP. *et al.* Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. *Nat Commun* 2020;**11**:1386.
48. Wang I-F, Guo B-S, Liu Y-C. *et al.* Autophagy activators rescue and alleviate pathogenesis of a mouse model with proteinopathies of the TAR DNA-binding protein 43. *Proc Natl Acad Sci* 2012;**109**:15024–15029.
49. Kumar S, Phaneuf D, Cordeau P. *et al.* Induction of autophagy mitigates TDP-43 pathology and translational repression of neurofilament mRNAs in mouse models of ALS/FTD. *Mol Neurodegener* 2021;**16**:1.
50. Chu Y-P, Jin L-W, Wang L-C. *et al.* Transthyretin attenuates TDP-43 proteinopathy by autophagy activation via ATF4 in FTLD-TDP. *Brain* 2023;**146**:2089–2106.
51. Tanaka Y, Ito S, Suzuki G. TDP-43 secretion via extracellular vesicles is regulated by macroautophagy. *Autophagy Rep* 2024;**3**:2291250.
52. Heiseke A, Aguib Y, Riemer C. *et al.* Lithium induces clearance of protease resistant prion protein in prion-infected cells by induction of autophagy. *J Neurochem* 2009;**109**:25–34.
53. Jeong J-K, Moon M-H, Bae B-C. *et al.* Autophagy induced by resveratrol prevents human prion protein-mediated neurotoxicity. *Neurosci Res* 2012;**73**:99–105.
54. Thellung S, Scoti B, Corsaro A. *et al.* Pharmacological activation of autophagy favors the clearing of intracellular aggregates of misfolded prion protein peptide to prevent neuronal death. *Cell Death Dis* 2018;**9**:1–15.
55. de la Cueva M, Antequera D, Ordoñez-Gutierrez L. *et al.* Amyloid-β impairs mitochondrial dynamics and autophagy in Alzheimer's disease experimental models. *Sci Rep* 2022; **12**:10092.
56. Zhang W, Xu C, Sun J. *et al.* Impairment of the autophagy–lysosomal pathway in Alzheimer's diseases: pathogenic mechanisms and therapeutic potential. *Acta Pharm Sin B* 2022;**12**: 1019–1040.
57. Mani S, Swargiary G, Singh M. *et al.* Mitochondrial defects: an emerging theranostic avenue towards Alzheimer's associated dysregulations. *Life Sci* 2021;**285**:119985.
58. Lee J-H, Yang D-S, Goulbourne CN. *et al.* Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nat Neurosci* 2022;**25**:688–701.
59. Feng Q, Luo Y, Zhang X-N. *et al.* MAPT/tau accumulation represses autophagy flux by disrupting IST1-regulated ESCRT-III complex formation: a vicious cycle in Alzheimer neurodegeneration. *Autophagy* 2020;**16**:641–658.
60. Piras A, Collin L, Grüninger F. *et al.* Autophagic and lysosomal defects in human tauopathies: analysis of post-mortem brain from patients with familial Alzheimer disease, corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol Commun* 2016;**4**:22.
61. Ashkenazi A, Bento CF, Ricketts T. *et al.* Polyglutamine tracts regulate beclin 1-dependent autophagy. *Nature* 2017;**545**: 108–111.
62. Ferrari L, Bauer B, Qiu Y. *et al.* Tau fibrils evade autophagy by excessive p62 coating and TAX1BP1 exclusion. Science. *Advances* 2024;**10**:eadm8449.
63. Zhao DY, Bäuerlein FJB, Saha I. *et al.* Autophagy preferentially degrades non-fibrillar polyQ aggregates. *Mol Cell* 2024;**84**:1980–1994.e8.
64. Tang Q, Gao P, Arzberger T. *et al.* Alpha-Synuclein defects autophagy by impairing SNAP29-mediated autophagosome-lysosome fusion. *Cell Death Dis* 2021;**12**:1–16.
65. Khan MR, Yin X, Kang S-U. *et al.* Enhanced mTORC1 signaling and protein synthesis in pathologic α-synuclein cellular and animal models of Parkinson's disease. *Sci Transl Med* 2023;**15**:eadd0499.
66. Hou X, Chen TH-Y, Koga S. *et al.* Alpha-synuclein-associated changes in PINK1-PRKN-mediated mitophagy are disease context dependent. *Brain Pathol* 2023;**33**:e13175.
67. Stojkovska I, Wani WY, Zunke F. *et al.* Rescue of α-synuclein aggregation in Parkinson's patient neurons by synergistic enhancement of ER proteostasis and protein trafficking. *Neuron* 2022;**110**:436–451.e11.
68. Xia Q, Wang H, Hao Z. *et al.* TDP-43 loss of function increases TFEB activity and blocks autophagosome–lysosome fusion. *EMBO J* 2016;**35**:121–142.
69. Leibiger C, Deisel J, Aufschnaiter A. *et al.* TDP-43 controls lysosomal pathways thereby determining its own clearance and cytotoxicity. *Hum Mol Genet* 2018;**27**:1593–1607.
70. López-Pérez Ó, Otero A, Filali H. *et al.* Dysregulation of autophagy in the central nervous system of sheep naturally infected with classical scrapie. *Sci Rep* 2019;**9**:1911.
71. Moon J-H, Lee J-H, Nazim UM. *et al.* Human prion protein-induced autophagy flux governs neuron cell damage in primary neuron cells. *Oncotarget* 2016;**7**:29989–30002.
72. Stamatakou E, Wróbel L, Hill SM. *et al.* Mendelian neurodegenerative disease genes involved in autophagy. *Cell Discov* 2020;**6**: 1–13.
73. Yamamoto H, Zhang S, Mizushima N. Autophagy genes in biology and disease. *Nat Rev Genet* 2023;**24**:382–400.
74. Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med* 2012;**2**:a006171.
75. Lee J-H, Yu WH, Kumar A. *et al.* Lysosomal proteolysis and autophagy require Presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell* 2010;**141**:1146–1158.
76. Li L, Kim HJ, Roh JH. *et al.* Pathological manifestation of the induced pluripotent stem cell-derived cortical neurons from an early-onset Alzheimer's disease patient carrying a presenilin-1 mutation (S170F). *Cell Prolif* 2020;**53**:e12798.
77. Luo R, Fan Y, Yang J. *et al.* A novel missense variant in ACAA1 contributes to early-onset Alzheimer's disease, impairs lysosomal function, and facilitates amyloid-β pathology and cognitive decline. *Sig Transduct Target Ther* 2021;**6**:1–16.
78. Dawson TM, Dawson VL. The role of parkin in familial and sporadic Parkinson's disease. *Mov Disord* 2010;**25**: S32–S39.
79. Vizziello M, Borellini L, Franco G. *et al.* Disruption of mitochondrial homeostasis: the role of PINK1 in Parkinson's disease. *Cells* 2021;**10**:3022.
80. Valente EM, Abou-Sleiman PM, Caputo V. *et al.* Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 2004;**304**:1158–1160.
81. Foster AD, Rea SL. The role of sequestosome 1/p62 protein in amyotrophic lateral sclerosis and frontotemporal dementia pathogenesis. *Neural Regen Res* 2020;**15**:2186–2194.
82. Gallagher ER, Holzbaur ELF. The selective autophagy adaptor p62/SQSTM1 forms phase condensates regulated by HSP27

that facilitate the clearance of damaged lysosomes via lysophagy. *Cell Rep* 2023;**42**:112037.
83. Brennan A, Layfield R, Long J. *et al.* An ALS-associated variant of the autophagy receptor SQSTM1/p62 reprograms binding selectivity toward the autophagy-related hATG8 proteins. *J Biol Chem* 2022;**298**:101514.
84. Foster A, Scott D, Layfield R. *et al.* An FTLD-associated SQSTM1 variant impacts Nrf2 and NF-κB signalling and is associated with reduced phosphorylation of p62. *Mol Cell Neurosci* 2019;**98**: 32–45.
85. Kwon DH, Park OH, Kim L. *et al.* Insights into degradation mechanism of N-end rule substrates by p62/SQSTM1 autophagy adapter. *Nat Commun* 2018;**9**:3291.
86. Fecto F, Yan J, Vemula SP. *et al.* SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. *Arch Neurol* 2011;**68**: 1440–1446.
87. Bartolome F, Esteras N, Martin-Requero A. *et al.* Pathogenic p62/SQSTM1 mutations impair energy metabolism through limitation of mitochondrial substrates. *Sci Rep* 2017;**7**:1666.
88. Usategui-Martín R, Gestoso-Uzal N, Calero-Paniagua I. *et al.* A mutation in p62 protein (p. R321C), associated to Paget's disease of bone, causes a blockade of autophagy and an activation of NF-kB pathway. *Bone* 2020;**133**:115265.
89. Cavey JR, Ralston SH, Hocking LJ. *et al.* Loss of ubiquitin-binding associated with Paget's disease of bone p62 (SQSTM1) mutations. *J Bone Miner Res* 2005;**20**:619–624.
90. Kwok CT, Morris A, de Belleroche JS. Sequestosome-1 (SQSTM1) sequence variants in ALS cases in the UK: prevalence and coexistence of SQSTM1 mutations in ALS kindred with PDB. *Eur J Hum Genet* 2014;**22**:492–496.
91. Carroll B, Otten EG, Manni D. *et al.* Oxidation of SQSTM1/p62 mediates the link between redox state and protein homeostasis. *Nat Commun* 2018;**9**:256.
92. Goode A, Rea S, Sultana M. *et al.* ALS-FTLD associated mutations of SQSTM1 impact on Keap1-Nrf2 signalling. *Mol Cell Neurosci* 2016;**76**:52–58.
93. Zhao S, Chen R, Gao Y. *et al.* Fundamental roles of the Optineurin gene in the molecular pathology of amyotrophic lateral sclerosis. *Front Neurosci* 2023;**17**:1319706.
94. Shen W-C, Li H-Y, Chen G-C. *et al.* Mutations in the ubiquitin-binding domain of OPTN/optineurin interfere with autophagy-mediated degradation of misfolded proteins by a dominant-negative mechanism. *Autophagy* 2015;**11**: 685–700.
95. Wong YC, Holzbaur ELF. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. *Proc Natl Acad Sci* 2014;**111**:E4439–E4448.
96. Maruyama H, Morino H, Ito H. *et al.* Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* 2010;**465**:223–226.
97. Chernyshova K, Inoue K, Yamashita S-I. *et al.* Glaucoma-associated mutations in the Optineurin gene have limited impact on parkin-dependent Mitophagy. *Invest Ophthalmol Vis Sci* 2019;**60**:3625–3635.
98. Khatoon F, Kumar V, Anjum F. *et al.* Frustration analysis of TBK1 missense mutations reported in ALS/FTD and cancer patients. *3 Biotech* 2022;**12**:174.
99. Harding O, Evans CS, Ye J. *et al.* ALS- and FTD-associated missense mutations in TBK1 differentially disrupt mitophagy. *Proc Natl Acad Sci USA* 2021;**118**:e2025053118.
100. Brenner D, Sieverding K, Srinidhi J. *et al.* A TBK1 variant causes autophagolysosomal and motoneuron pathology without neuroinflammation in mice. *J Exp Med* 2024;**221**:e20221190.
101. Talaia G, Bentley-DeSousa A, Ferguson SM. Lysosomal TBK1 responds to amino acid availability to relieve Rab7-dependent mTORC1 inhibition. *EMBO J* 2024;**43**:3948–3967.
102. Richter B, Sliter DA, Herhaus L. *et al.* Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. *Proc Natl Acad Sci* 2016;**113**:4039–4044.
103. Porras G, Ruiz S, Maestro I. *et al.* Functional characterization of a familial ALS-associated missense TBK1 (p-Arg573Gly) mutation in patient-derived Lymphoblasts. *Int J Mol Sci* 2023;**24**:2847.
104. Freischmidt A, Wieland T, Richter B. *et al.* Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. *Nat Neurosci* 2015;**18**:631–636.
105. Ye J, Cheung J, Gerbino V. *et al.* Effects of ALS-associated TANK binding kinase 1 mutations on protein–protein interactions and kinase activity. *Proc Natl Acad Sci* 2019;**116**:24517–24526.
106. de Majo M, Topp SD, Smith BN. *et al.* ALS-associated missense and nonsense TBK1 mutations can both cause loss of kinase function. *Neurobiol Aging* 2018;**71**:266.e1–266.e10.
107. Cirulli ET, Lasseigne BN, Petrovski S. *et al.* Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. *Science* 2015;**347**:1436–1441.
108. Gerbino V, Kaunga E, Ye J. *et al.* The loss of TBK1 kinase activity in motor neurons or in all cell types differentially impacts ALS disease progression in SOD1 mice. *Neuron* 2020;**106**:789–805.e5.
109. Davidson JM, Wu SSL, Rayner SL. *et al.* The E3 ubiquitin ligase SCF cyclin F promotes Sequestosome-1/p62 insolubility and foci formation and is dysregulated in ALS and FTD pathogenesis. *Mol Neurobiol* 2023;**60**:5034–5054.
110. Ma Q, Xin J, Peng Q. *et al.* UBQLN2 and HSP70 participate in parkin-mediated mitophagy by facilitating outer mitochondrial membrane rupture. *EMBO Rep* 2023;**24**:e55859.
111. Sung H, Lloyd TE. Disrupted endoplasmic reticulum-mediated autophagosomal biogenesis in a drosophila model of C9-ALS-FTD. *Autophagy* 2024;**20**:94–113.
112. Zhang S, Tong M, Zheng D. *et al.* C9orf72-catalyzed GTP loading of Rab39A enables HOPS-mediated membrane tethering and fusion in mammalian autophagy. *Nat Commun* 2023;**14**:6360.
113. Beckers J, Tharkeshwar AK, Fumagalli L. *et al.* A toxic gain-of-function mechanism in C9orf72 ALS impairs the autophagy-lysosome pathway in neurons. *Acta Neuropathol Commun* 2023;**11**:151.
114. Funes S, Jung J, Gadd DH. *et al.* Expression of ALS-PFN1 impairs vesicular degradation in iPSC-derived microglia. *Nat Commun* 2024;**15**:2497.
115. Kawajiri S, Saiki S, Sato S. *et al.* Genetic mutations and functions of PINK1. *Trends Pharmacol Sci* 2011;**32**:573–580.
116. Woodroof HI, Pogson JH, Begley M. *et al.* Discovery of catalytically active orthologues of the Parkinson's disease kinase PINK1: analysis of substrate specificity and impact of mutations. *Open Biol* 2011;**1**:110012.
117. Grünewald A, Gegg ME, Taanman J-W. *et al.* Differential effects of PINK1 nonsense and missense mutations on mitochondrial function and morphology. *Exp Neurol* 2009;**219**:266–273.
118. Peng W, Schröder LF, Song P. *et al.* Parkin regulates amino acid homeostasis at mitochondria-lysosome (M/L) contact sites in Parkinson's disease. *Sci Adv* 2023;**9**:eadh3347.
119. Broadway BJ, Boneski PK, Bredenberg JM. *et al.* Systematic functional analysis of PINK1 and PRKN coding variants. *Cells* 2022;**11**:2426.
120. Yi W, MacDougall EJ, Tang MY. *et al.* The landscape of parkin variants reveals pathogenic mechanisms and therapeutic targets in Parkinson's disease. *Hum Mol Genet* 2019;**28**:2811–2825.

121. Sriram SR, Li X, Ko HS. *et al.* Familial-associated mutations differentially disrupt the solubility, localization, binding and ubiquitination properties of parkin. *Hum Mol Genet* 2005;**14**: 2571–2586.
122. Spratt DE, Julio Martinez-Torres R, Noh YJ. *et al.* A molecular explanation for the recessive nature of parkin-linked Parkinson's disease. *Nat Commun* 2013;**4**:1983.
123. Hanss Z, Larsen SB, Antony P. *et al.* Mitochondrial and clearance impairment in p.D620N VPS35 patient-derived neurons. *Mov Disord* 2021;**36**:704–715.
124. Navarro-Romero A, Fernandez-Gonzalez I, Riera J. *et al.* Lysosomal lipid alterations caused by glucocerebrosidase deficiency promote lysosomal dysfunction, chaperone-mediated-autophagy deficiency, and alpha-synuclein pathology. *npj Parkinsons Dis* 2022;**8**:1–15.
125. Mubariz F, Saadin A, Lingenfelter N. *et al.* Deregulation of mTORC1-TFEB axis in human iPSC model of GBA1-associated Parkinson's disease. *Front Neurosci* 2023;**17**:1152503.
126. Metzger S, Saukko M, Van Che H. *et al.* Age at onset in Huntington's disease is modified by the autophagy pathway: implication of the V471A polymorphism in Atg7. *Hum Genet* 2010;**128**:453–459.
127. Metzger S, Walter C, Riess O. *et al.* The V471A polymorphism in autophagy-related gene ATG7 modifies age at onset specifically in Italian Huntington disease patients. *PLoS One* 2013;**8**:e68951.
128. Baselli GA, Jamialahmadi O, Pelusi S. *et al.* Rare ATG7 genetic variants predispose patients to severe fatty liver disease. *J Hepatol* 2022;**77**:596–606.
129. Ma KY, Fokkens MR, van Laar T. *et al.* Systematic analysis of PINK1 variants of unknown significance shows intact mitophagy function for most variants. *NPJ Parkinsons Dis* 2021; **7**:113.
130. Sharma K, Kishore A, Lechado-Terradas A. *et al.* A novel PINK1 p.F385S loss-of-function mutation in an Indian family with Parkinson's disease. *Mov Disord* 2024;**39**:1217–1225.
131. Shiraishi T, Bono K, Hiraki H. *et al.* The impact of VPS35 D620N mutation on alternative autophagy and its reversal by estrogen in Parkinson's disease. *Cell Mol Life Sci* 2024;**81**:103.
132. Oh YM, Lee SW, Kim WK. *et al.* Age-related Huntington's disease progression modeled in directly reprogrammed patient-derived striatal neurons highlights impaired autophagy. *Nat Neurosci* 2022;**25**:1420–1433.
133. Mackenzie IRA, Bigio EH, Ince PG. *et al.* Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. *Ann Neurol* 2007;**61**:427–434.
134. Osaka M, Ito D, Yagi T. *et al.* Evidence of a link between ubiquilin 2 and optineurin in amyotrophic lateral sclerosis. *Hum MolGenet* 2015;**24**:1617–1629.
135. Oakes JA, Davies MC, Collins MO. TBK1: a new player in ALS linking autophagy and neuroinflammation. *Molecular Brain* 2017;**10**:5.
136. Catanese A, Olde Heuvel F, Mulaw M. *et al.* Retinoic acid worsens ATG10-dependent autophagy impairment in TBK1-mutant hiPSC-derived motoneurons through SQSTM1/p62 accumulation. *Autophagy* 2019;**15**:1719–1737.
137. Freischmidt A, Müller K, Ludolph AC. *et al.* Association of Mutations in TBK1 with sporadic and familial amyotrophic lateral sclerosis and frontotemporal dementia. *JAMA Neurol* 2017;**74**: 110–113.
138. Shao W, Todd TW, Wu Y. *et al.* Two FTD-ALS genes converge on the endosomal pathway to induce TDP-43 pathology and degeneration. *Science* 2022;**378**:94–99.
139. Heckmann BL, Green DR. LC3-associated phagocytosis at a glance. *J Cell Sci* 2019;**132**:jcs222984.
140. New J, Thomas SM. Autophagy-dependent secretion: mechanism, factors secreted, and disease implications. *Autophagy* 2019;**15**:1682–1693.
141. Hartmann J, Bajaj T, Otten J. *et al.* SKA2 regulated hyperactive secretory autophagy drives neuroinflammation-induced neurodegeneration. *Nat Commun* 2024;**15**:2635.
142. Cui M, Yoshimori T, Nakamura S. Autophagy system as a potential therapeutic target for neurodegenerative diseases. *Neurochem Int* 2022;**155**:105308.
143. Menzies FM, Fleming A, Caricasole A. *et al.* Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. *Neuron* 2017;**93**:1015–1034.
144. Rubinsztein DC, Bento CF, Deretic V. Therapeutic targeting of autophagy in neurodegenerative and infectious diseases. *J Exp Med* 2015;**212**:979–990.
145. Jiang T, Yu J-T, Zhu X-C. *et al.* Temsirolimus attenuates tauopathy in vitro and in vivo by targeting tau hyperphosphorylation and autophagic clearance. *Neuropharmacology* 2014;**85**: 121–130.
146. Xie P-L, Zheng M-Y, Han R. *et al.* Pharmacological mTOR inhibitors in ameliorating Alzheimer's disease: current review and perspectives. *Front Pharmacol* 2024;**15**:1366061.
147. Davoody S, Asgari Taei A, Khodabakhsh P. *et al.* mTOR signaling and Alzheimer's disease: what we know and where we are? *CNS Neurosci Ther* 2024;**30**:e14463.
148. Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. *Nat Aging* 2023;**3**:642–660.
149. Moskal N, Riccio V, Bashkurov M. *et al.* ROCK inhibitors upregulate the neuroprotective parkin-mediated mitophagy pathway. *Nat Commun* 2020;**11**:88.
150. Koch JC, Leha A, Bidner H. *et al.* Safety, tolerability, and efficacy of fasudil in amyotrophic lateral sclerosis (ROCK-ALS): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2024;**23**:1133–1146.

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