AMERICAN SOCIETY FOR MICROBIOLOGY | Molecular and Cellular Biology®

MINIREVIEW

Endosomal Trafficking in Alzheimer's Disease, Parkinson's Disease, and Neuronal Ceroid Lipofuscinosis

Yasir H. Qureshi,[a] Penelope Baez,[a] Christiane Reitz[a,b,c,d]

[a]The Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, New York, USA
[b]The Gertrude H. Sergievsky Center, Columbia University, New York, New York, USA
[c]Department of Neurology, Columbia University, New York, New York, USA
[d]Department of Epidemiology, Columbia University, New York, New York, USA

Yasir H. Qureshi and Penelope Baez contributed equally to this work. The order of their names was decided based on the contribution of both authors to design and content of the manuscript.

ABSTRACT Neuronal ceroid lipofuscinosis (NCL) is one of the most prevalent neurodegenerative disorders of early life, Parkinson's disease (PD) is the most common neurodegenerative disorder of midlife, while Alzheimer's disease (AD) is the most common neurodegenerative disorder of late life. While they are phenotypically distinct, recent studies suggest that they share a biological pathway, retromer-dependent endosomal trafficking. A retromer is a multimodular protein assembly critical for sorting and trafficking cargo out of the endosome. As a lysosomal storage disease, all 13 of NCL's causative genes affect endolysosomal function, and at least four have been directly linked to retromer. PD has several known causative genes, with one directly linked to retromer and others causing endolysosomal dysfunction. AD has over 25 causative genes/risk factors, with several of them linked to retromer or endosomal trafficking dysfunction. In this article, we summarize the emerging evidence on the association of genes causing NCL with retromer function and endosomal trafficking, review the recent evidence linking NCL genes to AD, and discuss how NCL, AD, and PD converge on a shared molecular pathway. We also discuss this pathway's role in microglia and neurons, cell populations which are critical to proper brain homeostasis and whose dysfunction plays a key role in neurodegeneration.

KEYWORDS Alzheimer's disease (AD), endocytic pathway, endosomal trafficking, genetic and cell biology findings on Alzheimer's disease, microglia, NCL genes, Parkinson's disease, retromer defects, retromer proteins (Vps35, Vps26, Vos29), retromer viral vectors for AD gene therapy

Alzheimer's disease (AD) is a neurodegenerative disease that progressively destroys memory and thinking skills and disrupts behavior, ultimately leading to complete dependency and death. It is the most common type of dementia among individuals 65 or older (1). Currently, more than 5.5 million Americans are living with AD, and this number is expected to triple by the year 2050 (2). While the majority of cases occur beyond age 65, 5 to 10% of cases show an early-onset form, with clinical onset between 30 and 50 years of age (3). Key pathological hallmarks are extracellular diffuse and neuritic amyloid plaques composed of abnormally folded Aβ40 and Aβ42 and intraneuronal accumulation of neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein (p-tau), often accompanied by neuropil threads, dystrophic neurites, associated astrogliosis, microglial activation, and cerebral amyloid angiopathy (4). These changes commonly show a specific spatial/temporal profile initiating in entorhinal cortex and then spreading to other areas of the brain (5).

Ten percent of these early-onset AD cases are explained by known mutations in the

Citation Qureshi YH, Baez P, Reitz C. 2020. Endosomal trafficking in Alzheimer's disease, Parkinson's disease, and neuronal ceroid lipofuscinosis. Mol Cell Biol 40:e00262-20. https://doi.org/10.1128/MCB.00262-20.

Address correspondence to Christiane Reitz, cr2101@cumc.columbia.edu.

Accepted manuscript posted online 20 July 2020
Published

presinilin 1 (PSEN1), presinilin 2 (PSEN2), and amyloid precursor protein (APP) genes (3). The apolipoprotein E gene (*APOE*) poses the strongest risk factor for the late-onset form (6, 7). In addition, large-scale genomic studies conducted over the past 10 years have identified over 25 genes modulating AD susceptibility (8, 9). Notably, these genes cluster predominantly in specific molecular pathways, in particular lipid metabolism, inflammation/immune response, endocytosis, and intracellular trafficking (8–10).

The second most prevalent neurodegenerative disease, Parkinson's disease (PD), affects 1% to 2% of the population and is characterized by resting tremor, rigidity, and bradykinesia, along with memory impairments and other behavior changes (11, 12). PD pathology, characterized in particular by progressive loss of dopaminergic (DA) neurons in the substantia nigra, usually initiates in the basal ganglia, with involvement of cerebellum thalamus, hypothalamus, and limbic system (13–16). Several genes have been associated with PD (*LRRK2*, *GBA*, *PRKN*, *SNCA*, *MAPT*, *EIF4G1*, *DNAJC13*, *CHCHD2*, *PINK1*, and *PARK7*). Notably, some of these have been implicated in endolysosomal dysfunction (11–13, 17–21).

A master conductor of endosomal sorting and trafficking is the retromer complex (22). Retromer recognizes specific transmembrane proteins and exports them to their appropriate destinations within the cell. It facilitates this transport by forming tubules. Protein cargo from the endosomes can be exported to three possible destinations: retrograde transport to the *trans*-Golgi network (TGN), recycling to the plasma membrane, and sorting to the lysosomes for degradation. The former two are controlled by retromer (22–24). The retromer complex is composed of multiple modules, with the two central components being the cargo recognition module (CRM) and the tubulation module (SNX-BAR). The CRM consists of three largely globular proteins, VPS35, VPS26, and VPS29, named after the vacuolar protein-sorting genes in yeast. The tubulation module comprises heterodimers of the BAR domain-containing sorting nexins SNX1/SNX2 and SNX5/SNX6 (23, 25–27).

Retromer and endolysosomal dysfunction have been firmly established in the etiology of both AD and PD (28–38). The first evidence for an association with AD came from a model-guided microarray study showing a reduction of VPS26 and VPS35 in brain regions affected by the disease (39), followed by the identification of *SORL1* (a retromer cargo receptor) (40) as a risk gene for AD and demonstrating that SORL1 is critical for trafficking of APP away from amyloidogenic pathways and recycling it back to the cell surface (41, 42). A series of subsequent genetic studies firmly confirmed *SORL1* in both early- and late-onset AD (41, 43–45) and have linked several additional retromer core proteins to AD; among these are SNX1, SNX3, and rab7a (26, 46). In line with this notion, there is evidence of endolysosomal dysfunction starting early in entorhinal cortex and hippocampus in AD brains with enlargement of endosomes (39, 47–49). The strongest genetic risk factor for sporadic AD, APOE4, is also associated with enlargement of endosomes and their dysfunction in an age-dependent manner (50–53). In early-onset PD, mutations in PRKN (parkin) lead to autosomal recessive early-onset PD (54), with loss of parkin function, increased formation of intraluminal vesicles coupled with enhanced release of exosomes, decreased endosomal tubulation, and membrane association of vesicle protein sorting 35 (VPS35) and sorting nexin 1 (SNX1), as well as decreased mannose 6 phosphate receptor (M6PR), in line with impairment of retromer pathway in parkin-deficient cells. In addition, a rare mutation in the retromer gene *VPS35* (*D620N*) is associated with risk of PD (28–36), supporting a role of retromer-dependent trafficking and endolysosomal function.

In addition to these AD-associated retromer genes and proteins, over the past few years an additional set of genes has been linked to retromer function and AD. Among these were a small number of experimental, cell biology, and animal studies reporting genes implicated in neuronal ceroid lipofuscinosis (NCL) (55), a genetically determined lysosomal storage disorder. It has been demonstrated that retromer is essential in the delivery of certain hydrolytic enzymes to lysosomes, and its deficiency leads to the accumulation of dysfunctional autolysosomes (56, 57).

CLINICAL AND MORPHOLOGICAL CHARECTERISTICS OF NCL

NCL is morphologically characterized by cellular lipopigment inclusions, neuronal loss, and progressive neurodegeneration (58). The childhood forms present clinically as progressive mental and motor deterioration and loss of vision with shortened life expectancy, while the rare adult-onset forms are dominated by dementia. To date, 13 genetically distinct forms of NCL have been identified (Table 1), all characterized by the accumulation of abnormal lipofuscin-like material in the lysosomes of nerve cells, associated with progressive and selective destruction of neurons, particularly in the cerebral and cerebellar cortex and in the retina (58–61). Historically, NCL has been classified into four distinctive forms, based on the clinical manifestation, morphologic features, and age of onset: infantile (INCL), late-infantile (LINCL), juvenile (JNLC), and adult type NCL (ANLC) (59).

NEURONAL CEROID LIPOFUSCINOSIS AND RETROMER

Of the 13 genes causing NCL, four have been linked to retromer function: *CLN1*, *CLN3*, *CLN5*, and *CLN10* (cathepsin D, or CTSD) (55, 61–66). These NCL variants cause pathological changes that seem to share an endolysosomal dysfunctional pathway. CLN10 disease presents as congenital or early infantile neuronal ceroid lipofuscinosis disease and is caused by mutations in *CTSD*, encoding cathepsin D (67–69). Cathepsin D is a lysosomal protease that is highly expressed in the brain (70). CTSD shows pepsin-like activity and has an important role in protein turnover and activation of hormones and growth factors through proteolysis. Retromer plays a vital role in CTSD processing. Procathepsin D is transported by cation-independent mannose 6-phosphate receptor (CI-M6PR) or sortilin to the endosome, where it is processed to the mature cathepsin D (71–74). Retromer, in turn, mediates trafficking of sortilin and CI-M6PR out of the endosomal-lysosomal system and prevents their degradation (72–75). Alterations in CTSD protein and mRNA levels have been demonstrated in AD (71, 76–78), and CTSD deficiency has been shown to promote tau neurotoxicity, likely through a mechanistic defect in endosomal-lysosomal trafficking (76, 79–81).

Juvenile CLN3 disease is characterized by early vision loss at around 6 years of age with cognitive decline followed by seizures, psychosis, and motor dysfunction (82–84). The *CLN3* gene encodes a palmitoyl-protein delta-9 desaturase protein, which also modulates lysosomal transport and function (85, 86). CLN3 protein has been implicated in retrograde transport of cargo from the endosome to the Golgi compartment by modulating SNARE phosphorylation and assembly (87–89), and a recent investigation by Yasa and Lefrancois established that CLN3 protein plays a key role in facilitating the interaction between Rab7A, retromer, and sortilin (63). Rab7A belongs to the family of Rab GTPases proteins that is active at endosomal membranes and has been involved in endosome-to-TGN trafficking, retromer recruitment, autophagosome-lysosome fusion, lysosomal positioning, and degradation of endocytic cargo (62, 78, 90–92). In the absence of wild-type CLN3, CI-M6PR and sortilin receptors are degraded, which in turn leads to impaired CTSD processing (63).

The *CLN5* gene is implicated in late infantile NCL, a type of NCL that affects children between ages 2 and 4 and has a very high mortality. In the mouse brain, *CLN5* is expressed in cortical neurons, hippocampal pyramidal neurons, hypothalamus, and cerebellum (93); the highest levels, however, have been detected in microglial cells (55, 94). CLN5 protein undergoes posttranslational modifications that include glycosylation and cleavage (95, 96). The depletion of CLN5 leads to lysosomal degradation of the retromer receptors sortilin and CI-M6PR (62). In the absence of CLN5, Rab7 is not activated, VPS26 is not recruited to endosomes, and sortilin and CI-M6PR receptors are degraded in lysosomes (62). Glycosylation defects result in ER mislocalization of CLN5, which results in a loss of function and ER stress (55, 97). CLN5 is usually localized to the endolysosomal compartment, and it is also secreted into the extracellular space (55, 95, 98, 99).

Using whole-exome sequencing, we recently identified a rare missense variant of *CLN5* (rs199609750; c.A959G; population frequency, 7.418e−05) that segregates with

TABLE 1 Genes and proteins implicated in NCL and their association with retromer function and/or Alzheimer's disease[a]

Gene	Protein	Protein function(s) (reference[s])	NCL clinical phenotype(s)	AD association(s) (reference[s])	Retromer or endosomal trafficking association(s) (reference[s])
CLN1	Palmitoyl protein thiosterase 1 (PPT1)	Removes palmitic acid from S-acylated proteins (137, 138)	Infantile, juvenile, adult	Metabolic clearance of Aβ in early stages of AD (105); disruption of protein palmitoylation/depalmitoylation balance is associated with AD (106–108)	Transported to lysosomes by mannose 6-phosphate receptor (64–66)
CLN2	Tripeptidyl-peptidase 1 (TPP1)	Lysosomal serine protease; also has endopeptidase activity (139–142)	Late infantile	Destabilizes Aβ fibrils in lysosomes through multiple proteolytic cleavages within the β-sheet domain (115)	
CLN3	CLN3 (transmembrane protein)	Protein function has not been completely unraveled; has multiple lysosomal targeting signals; activates Rab7; implicated in a complex interaction of cytoskeleton with endocytic membrane trafficking (82)	Juvenile		Retrograde transport of cargo from endosome to Golgi compartment by modulating SNARE phosphorylation and assembly (87–89); also mediates Rab7A–PLEKHM1 interaction (63)
CLN4 (*DNAJC5*)	Cysteine-string protein alpha (CSPα)	Active at synapses, regulates exocytosis and other proteins involved in secretion dynamics (143–146)	Adult		
CLN5	CLN5	Secreted glycoprotein that might act as glycoside hydrolase in amoeba and may interact with CLN10 and CLN3 (147, 148); may also have a role in embryonic development of interneurons (149), in mitochondrial function (150), and in autophagy (151)	Late infantile, juvenile	Rare missense variant mutation of *CLN5* gene segregated with AD status in multiplex families (55)	Recruitment of Rab7A and retromer to the endosomal membrane (62); AD variant leads to altered processing of cathepsin D and APP (55)
CLN6	CLN6	Transmembrane protein of unknown function, localized at the endoplasmic reticulum (152)	Late infantile, adult		
CLN7	MFSD8	Unknown function	Late infantile, juvenile		
CLN8	CLN8	Unknown function	Late infantile		
CLN10	CLN10/cathepsin D (CTSD)	Aspartyl endopeptidase; major roles in endocytic, autophagic, and apoptotic degradation of proteins; highly expressed in brain tissue (70, 71)	Congenital late infantile, juvenile, adult	Changes in CTSD levels have been associated with AD (71, 76–78); CTSD deficiency associated with Tau toxicity in animal models (76, 79, 80)	Trafficked via sortilin or CI-M6PR to the endosomal-lysosomal system (71–74)
CLN11	Progranulin/proepithelin/ acrogranin (GRN)	Exact mechanism is unknown; has been proposed to act as neurotrophic factor and may be involved in biogenesis and function of lysosomes (153); also may play a role in microglial innate immunity in the CNS (124, 125, 153)	Adult	Associated with Aβ plaques, neurofibrillary tangles, tau phosphorylation, and increased CSF tau (118–121); also modulates lysosomal activity in neurons and glia leading to AD pathology (122, 123)	

(Continued on next page)

TABLE 1 (Continued)

Gene	Protein	Protein function(s) (reference[s])	NCL clinical phenotype(s)	AD association(s) (reference[s])	Retromer or endosomal trafficking association(s) (reference[s])
CLN12	CLN12/ATPase (p-type)/ 13A2/KRPPD/PARK9/ HSA9947/RP-37C10.4	Unknown function	Juvenile		
CLN13	Cathepsin F (CTSF)	Cysteine protease (58, 129)	Adult	Autosomal recessive CTSF gene variant was found in a clinically diagnosed early-onset AD family (130); a family with clinically suspected Kufs disease was shown to carry a novel *PSEN1* mutation (131); a homozygous mutation in CTSF was found in an early-onset AD case (73); biallelic mutations of CTSF have been linked to Kufs disease type B (28)	Associated with endosomal regulation and lysosomal trafficking through lysosomal integral membrane protein type 2 (LIMP-2) cleavage (129)
CLN14	Potassium channel tetramerization domain-containing protein 7 (KCTD7)	Unknown function	Infantile, late infantile		

[a]NCL, neuronal ceroid lipofuscinosis; AD, Alzheimer's disease; Aβ, amyloid beta; β, beta; SNARE, 4 alpha helix protein phosphorylation complex; Rab7A, Ras-nucleotide GTP-related protein; PLEKHM1, pleckstrin homology domain-containing family M member 1; CSF, cerebrospinal fluid. *PSEN1* gene, encodes presenilin-1 protein; ER, endoplasmic reticulum; CNS, central nervous system.

AD in multiplex families. Employing a combination of molecular biology, biochemistry, and immunofluorescence experiments, we validated that this *CLN5* AD variant is glycosylation deficient, which causes the expressed protein to be partially trapped in the ER, reduces its normal delivery to the endolysosomal system, and reduces its secretion. We also demonstrated that an effective deficiency in endosomal CLN5 caused by the missense variant results in a shift in the relative levels of procathepsin D, an established phenotype of retromer dysfunction (29, 71, 78, 100), and a reduction in the full-length APP. These studies further strengthen the findings from Mamo et al., who described the recruitment of retromer to the endosomal membrane by CLN5 and degradation of retromer trafficked receptors in lysosomes in the setting of CLN5 depletion, establishing that CLN5 deficiency translates into retromer's dysfunction (62). Since CLN5 is heavily enriched in microglia (94, 101), a cell type linked to AD, we postulate that the identified c.A959G missense mutant mediates its AD-associated toxicity by affecting retromer function in microglia. Microglia are activated upon tissue damage and are critical for brain homeostasis. The identification of *CLN5* as a microglial gene associated with AD is in line with the implication of the microglial gene *TREM2* as an AD susceptibility gene (102). Notably, retromer deficiency has been found in the microglia of AD brains (103), but the mechanisms underlying this deficiency are still unclear.

CLN1 disease primarily presents as infantile but has a broad age of onset, extending all the way into adulthood (104). The *CLN1* gene codes for palmitoyl-protein thioesterase 1 (PPT1), expressed in both neurons and microglia (105). PPT1 is a depalmitoylation enzyme, and, as such, a disruption of the protein palmitoylation/depalmitoylation balance is associated with AD (106–108). PPT1 has been implicated in endosomal trafficking (109, 110) and synaptic maintenance (110–112). In addition, PPT1 levels in the cell potentially can be influenced by retromer activity, since there is evidence that it is transported to lysosomes by the mannose 6-phosphate receptor (64–66). A study employing a proteomic approach in an APP^{NL-F} mouse model of AD found that PPT1 is upregulated and colocalizes with Aβ in this model. The authors conclude that PPT1 might have a role in Aβ clearance in the early stages of the disease, indicating that the upregulated expression of PPT1 is a compensatory mechanism resulting from elevated Aβ levels in early AD (105).

RECENT DEVELOPMENTS

A series of recent observations from human, animal, and cell biological studies provide additional evidence for an overlapping molecular etiology of AD and NCL. While it remains to be established if and how some or all of these links converge on the retromer pathway, the observed findings provide critical additional support for a shared molecular etiology of both syndromes.

AD pathology is characterized by the presence of Aβ protein oligomers, amyloid plaques (composed of insoluble fibrils), tau tangles, and neuroinflammation (113, 114). A recent study reported that microglial TPP1 protein (encoded by the *CLN2* gene) binds, digests, and causes destabilization of Aβ fibrils in the lysosomes through multiple proteolytic cleavages within the β-sheet domain (115).

The *CLN11* gene (alias *PGRN* or *GRN*), encoding progranulin (PGRN), has been linked to various neurodegenerative diseases, including NCL, frontotemporal lobar degeneration (FTLD), and AD (116, 117). Increased expression of *PGRN* has been documented in AD. PGRN is associated with Aβ plaques, neurofibrillary tangles, tau phosphorylation, and increased CSF tau levels (118–121). A microglial specific knockdown of PGRN results in malfunctioning phagocytic activity (116). A recent comprehensive review on PGRN discusses its role in lysosomal function in both neurons and microglia and argues that mutations in PGRN modulate lysosomal activity in both of these cell types, which in turn leads to AD pathology (122, 123). A global *PGRN* (i.e., *CLN11*) deletion can lead to an increase in lysosomal size and numbers in microglia, cd68 positivity, complement activation, and increased synaptic pruning (124). Microglial specific deletion of PGRN,

however, does not result in neuroinflammation, indicative of the fact that normal levels of neuronal PGRN play a significant role in preventing pathology in these mice (125).

Finally, *CLN13* (or *CTSF* gene) encodes cathepsin F protein, a soluble lysosomal cysteine protease (58). Mutations in the *CTSF* gene can cause Kufs disease type B, an adult form of NCL (126), where patients commonly present with epileptic seizures, ataxia, behavioral impairments, and dementia (127, 128). CTSF protein function has been linked to endosomal regulation and lysosomal trafficking through lysosomal integral membrane protein type 2 (LIMP-2) cleavage (129). Notably, an exome sequencing study in a consanguineous family with clinically diagnosed early-onset AD that previously tested negative for *PSEN1*, *PSEN2*, *APP*, *TAU*, *PGRN*, and *PRNP* mutations found an autosomal recessive *CTSF* gene variant (cG1243A:p Gly415Arg) (130). Vice versa, in a separate report, four members of a family with clinically suspected Kufs disease were shown to carry a novel *PSEN1* mutation (p.Leu381Phe). Carriers in this family developed dementia in their early 30s and showed neuropathological features of both Kufs and AD (131). These findings support the notion that NCL and AD are linked etiologically and clinically.

CONCLUSIONS

Several genes associated with NCL have now been linked to AD, and with *PSEN1* and *PRGRN* variants also being observed in families and individuals clinically presenting with NCL, evidence is mounting that these two syndromes overlap both etiologically and clinically.

The fact that at least 4 NCL genes have now been linked to endosomal trafficking, and that the major genomic studies on AD clearly identified endosomal trafficking as one of three major etiological pathways in AD (8–10, 22), strongly suggests a dysfunctional endolysosomal trafficking system as the shared molecular hub on which both disorders converge. Within the endolysosmal system, some of the molecular overlap seems to converge on retromer, suggesting that improving efficacy of the retromer trafficking pathway would decrease pathology in both syndromes. Additionally, brain transcriptome sequencing (RNA-seq) studies from the laboratory of B. Barres show that RNAs of most of the NCL-causing proteins discussed here are highly enriched in mouse microglia/macrophages (101, 132), whereas in humans these RNAs are enriched in mature astrocytes and microglia/macrophages, with the exception of CLN13, which has a considerable presence in human neurons as well (101, 132). These data, coupled with recent findings that retromer depletion in neurons leads to massive activation of microglia and astrocytes in mouse brains and that the astrogliosis can be partially rescued with retromer repletion using AAV (133), further support an interaction between NCL genes, endolysosomal trafficking, neurons, and glia. The fact that some of the genes associated with PD also have been implicated in endolysosomal dysfunction and retromer function (12, 13, 17, 20, 21, 28–36) further emphasizes the importance of the endolysosomal system and retromer in neurodegenerative disease, and it suggests that there is also at least a partial etiologic overlap with this disorder. Notably, particularly in Alzheimer's disease, the range of age of onset associated with disease-associated variants functioning in the endolysosomal pathway, for example, SORL1 (44), is significant, and enlargement of endosomes can be observed early in the disease process long before the onset of clinical symptoms (10), indicating that endolysosomal dysfunction in AD and PD can begin across a wide age range, likely even in early life.

Experimental, animal, and human studies are needed that comprehensively disentangle the molecular etiologies of NCL and AD, delineate their clinical subtypes, meticulously characterize their molecular and clinical overlap and association with retromer function, and delineate their etiologic overlap with other neurodegenerative disorders associated with retromer dysfunction, including PD. Studies on retromer enhancing pharmacological chaperones and retromer gene therapies have demonstrated that retromer function can be enhanced (133–136). While these studies have focused on adult-onset neurodegeneration (AD and PD), they provide proof of principle

and indicate that therapies targeting the retromer pathway also can benefit patients with NCL subtypes associated with retromer dysfunction.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health (NIH) grants RF1AG054080 (C.R. and P.B.), R01AG064614 (C.R.), U01AG052410 (C.R.), and P50AG008702 (C.R.).

We have no conflict of interest to declare.

REFERENCES

1. Lane CA, Hardy J, Schott JM. 2018. Alzheimer's disease. Eur J Neurol 25:59–70. https://doi.org/10.1111/ene.13439.
2. Anonymous. 2020. Alzheimer's disease fact sheet. National Institute on Aging, Bethesda, MD.
3. Cacace R, Sleegers K, Van Broeckhoven C. 2016. Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimers Dement 12:733–748. https://doi.org/10.1016/j.jalz.2016.01.012.
4. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. 2011. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1:a006189. https://doi.org/10.1101/cshperspect.a006189.
5. Braak H, Braak E. 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259. https://doi.org/10.1007/BF00308809.
6. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261:921–923. https://doi.org/10.1126/science.8346443.
7. Zhao N, Liu CC, Qiao W, Bu G. 2018. Apolipoprotein E, receptors, and modulation of Alzheimer's disease. Biol Psychiatry 83:347–357. https://doi.org/10.1016/j.biopsych.2017.03.003.
8. Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G, DeStefano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin C-F, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau M-T, Choi S-H, Reitz C, Pasquier F, Hollingworth P, Ramirez A, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fiévet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossù P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Naranjo MCD, et al. 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45:1452–1458. https://doi.org/10.1038/ng.2802.
9. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, van der Lee SJ, Amlie-Wolf A, Bellenguez C, Frizatti A, Chouraki V, Martin ER, Sleegers K, Badarinarayan N, Jakobsdottir J, Hamilton-Nelson KL, Moreno-Grau S, Olaso R, Raybould R, Chen Y, Kuzma AB, Hiltunen M, Morgan T, Ahmad S, Vardarajan BN, Epelbaum J, Hoffmann P, Boada M, Beecham GW, Garnier J-G, Harold D, Fitzpatrick AL, Valladares O, Moutet M-L, Gerrish A, Smith AV, Qu L, Bacq D, Denning N, Jian X, Zhao Y, Del Zompo M, Fox NC, Choi S-H, Mateo I, Hughes JT, Adams HH, Malamon J, Sanchez-Garcia F, Patel Y, Brody JA, Dombroski BA, Naranjo MCD, Daniilidou M, Eiriksdottir G, Mukherjee S, Wallon D, Uphill J, Aspelund T, Cantwell LB, Garzia F, Galimberti D, Hofer E, Butkiewicz M, Fin B, Scarpini E, Sarnowski C, Bush WS, Meslage S, Kornhuber J, White CC, Song Y, Barber RC, Engelborghs S, Sordon S, Voijnovic D, Adams PM, Vandenberghe R, Mayhaus M, Cupples LA, Albert MS, De Deyn PP, Gu W, Himali JJ, Beekly D, Squassina A, Hartmann AM, Orellana A, Blacker D, et al. 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. Nat Genet 51:414–430. https://doi.org/10.1038/s41588-019-0358-2.
10. Small SA, Simoes-Spassov S, Mayeux R, Petsko GA. 2017. Endosomal traffic jams represent a pathogenic hub and therapeutic target in Alzheimer's disease. Trends Neurosci 40:592–602. https://doi.org/10.1016/j.tins.2017.08.003.
11. Michael J Fox Foundation for Parkinson's Research. 2020. About Parkinson's: Parkinson's 101. https://www.michaeljfox.org/parkinsons-101.
12. Pang SY, Ho PW, Liu HF, Leung CT, Li L, Chang EES, Ramsden DB, Ho SL. 2019. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Transl Neurodegener 8:23. https://doi.org/10.1186/s40035-019-0165-9.
13. Simon DK, Tanner CM, Brundin P. 2020. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med 36:1–12. https://doi.org/10.1016/j.cger.2019.08.002.
14. Prakash KG, Bannur BM, Chavan MD, Saniya K, Sailesh KS, Rajagopalan A. 2016. Neuroanatomical changes in Parkinson's disease in relation to cognition: an update. J Adv Pharm Technol Res 7:123–126. https://doi.org/10.4103/2231-4040.191416.
15. Del Tredici K, Braak H. 2016. Review: sporadic Parkinson's disease: development and distribution of α-synuclein pathology. Neuropathol Appl Neurobiol 42:33–50. https://doi.org/10.1111/nan.12298.
16. Braak H, Braak E. 2000. Pathoanatomy of Parkinson's disease. J Neurol 247(Suppl 2):3–10. https://doi.org/10.1007/PL00007758.
17. Billingsley KJ, Bandres-Ciga S, Saez-Atienzar S, Singleton AB. 2018. Genetic risk factors in Parkinson's disease. Cell Tissue Res 373:9–20. https://doi.org/10.1007/s00441-018-2817-y.
18. Brunelli F, Valente EM, Arena G. 2020. Mechanisms of neurodegeneration in Parkinson's disease: keep neurons in the PINK1. Mech Ageing Dev 189:111277. https://doi.org/10.1016/j.mad.2020.111277.
19. Pascale E, Di Battista ME, Rubino A, Purcaro C, Valente M, Fattapposta F, Ferraguti G, Meco G. 2016. Genetic architecture of MAPT gene region in Parkinson disease subtypes. Front Cell Neurosci 10:96. https://doi.org/10.3389/fncel.2016.00096.
20. Arranz AM, Delbroek L, Van Kolen K, Guimarães MR, Mandemakers W, Daneels G, Matta S, Calafate S, Shaban H, Baatsen P, De Bock PJ, Gevaert K, Vanden Berghe P, Verstreken P, De Strooper B, Moechars D. 2015. LRRK2 functions in synaptic vesicle endocytosis through a kinase-dependent mechanism. J Cell Sci 128:541–552. https://doi.org/10.1242/jcs.158196.
21. Cookson MR. 2017. Mechanisms of mutant LRRK2 neurodegeneration. Adv Neurobiol 14:227–239. https://doi.org/10.1007/978-3-319-49969-7_12.
22. Small SA, Petsko GA. 2015. Retromer in Alzheimer disease, Parkinson disease and other neurological disorders. Nat Rev Neurosci 16:126–132. https://doi.org/10.1038/nrn3896.
23. Seaman MN. 2012. The retromer complex–endosomal protein recycling and beyond. J Cell Sci 125:4693–4702. https://doi.org/10.1242/jcs.103440.
24. McNally KE, Cullen PJ. 2018. Endosomal retrieval of cargo: retromer is not alone. Trends Cell Biol 28:807–822. https://doi.org/10.1016/j.tcb.2018.06.005.
25. Mukadam AS, Seaman MN. 2015. Retromer-mediated endosomal protein sorting: the role of unstructured domains. FEBS Lett 589:2620–2626. https://doi.org/10.1016/j.febslet.2015.05.052.
26. Brodin L, Shupliakov O. 2018. Retromer in synaptic function and pathology. Front Synaptic Neurosci 10:37. https://doi.org/10.3389/fnsyn.2018.00037.
27. Reitz C. 2015. The role of the retromer complex in aging-related neurodegeneration: a molecular and genomic review. Mol Genet Genomics 290:413–427. https://doi.org/10.1007/s00438-014-0939-9.
28. Zimprich A, Benet-Pagès A, Struhal W, Graf E, Eck SH, Offman MN,

Haubenberger D, Spielberger S, Schulte EC, Lichtner P, Rossle SC, Klopp N, Wolf E, Seppi K, Pirker W, Presslauer S, Mollenhauer B, Katzenschlager R, Foki T, Hotzy C, Reinthaler E, Harutyunyan A, Kralovics R, Peters A, Zimprich F, Brücke T, Poewe W, Auff E, Trenkwalder C, Rost B, Ransmayr G, Winkelmann J, Meitinger T, Strom TM. 2011. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet 89:168–175. https://doi.org/10.1016/j.ajhg.2011.06.008.

29. Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, Teasdale RD. 2014. The Vps35 D620N mutation linked to Parkinson's disease disrupts the cargo sorting function of retromer. Traffic 15:230–244. https://doi.org/10.1111/tra.12136.
30. McGough IJ, Steinberg F, Jia D, Barbuti PA, McMillan KJ, Heesom KJ, Whone AL, Caldwell MA, Billadeau DD, Rosen MK, Cullen PJ. 2014. Retromer binding to FAM21 and the WASH complex is perturbed by the Parkinson disease-linked VPS35(D620N) mutation. Curr Biol 24:1670–1676. https://doi.org/10.1016/j.cub.2014.06.024.
31. Tsika E, Glauser L, Moser R, Fiser A, Daniel G, Sheerin UM, Lees A, Troncoso JC, Lewis PA, Bandopadhyay R, Schneider BL, Moore DJ. 2014. Parkinson's disease-linked mutations in VPS35 induce dopaminergic neurodegeneration. Hum Mol Genet 23:4621–4638. https://doi.org/10.1093/hmg/ddu178.
32. Munsie LN, Milnerwood AJ, Seibler P, Beccano-Kelly DA, Tatarnikov I, Khinda J, Volta M, Kadgien C, Cao LP, Tapia L, Klein C, Farrer MJ. 2015. Retromer-dependent neurotransmitter receptor trafficking to synapses is altered by the Parkinson's disease VPS35 mutation p.D620N. Hum Mol Genet 24:1691–1703. https://doi.org/10.1093/hmg/ddu582.
33. Tang FL, Erion JR, Tian Y, Liu W, Yin DM, Ye J, Tang B, Mei L, Xiong WC. 2015. VPS35 in dopamine neurons is required for endosome-to-Golgi retrieval of Lamp2a, a receptor of chaperone-mediated autophagy that is critical for alpha-synuclein degradation and prevention of pathogenesis of Parkinson's disease. J Neurosci 35:10613–10628. https://doi.org/10.1523/JNEUROSCI.0042-15.2015.
34. Chen X, Kordich JK, Williams ET, Levine N, Cole-Strauss A, Marshall L, Labrie V, Ma J, Lipton JW, Moore DJ. 2019. Parkinson's disease-linked D620N VPS35 knockin mice manifest tau neuropathology and dopaminergic neurodegeneration. Proc Natl Acad Sci U S A 116:5765–5774. https://doi.org/10.1073/pnas.1814909116.
35. Ishizu N, Yui D, Hebisawa A, Aizawa H, Cui W, Fujita Y, Hashimoto K, Ajioka I, Mizusawa H, Yokota T, Watase K. 2016. Impaired striatal dopamine release in homozygous Vps35 D620N knock-in mice. Hum Mol Genet 25:4507–4517. https://doi.org/10.1093/hmg/ddw279.
36. Wang W, Wang X, Fujioka H, Hoppel C, Whone AL, Caldwell MA, Cullen PJ, Liu J, Zhu X. 2016. Parkinson's disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. Nat Med 22:54–63. https://doi.org/10.1038/nm.3983.
37. Nixon RA. 2017. Amyloid precursor protein and endosomal–lysosomal dysfunction in Alzheimer's disease: inseparable partners in a multifactorial disease. FASEB J 31:2729–2743. https://doi.org/10.1096/fj.201700359.
38. Song P, Trajkovic K, Tsunemi T, Krainc D. 2016. Parkin modulates endosomal organization and function of the endo-lysosomal pathway. J Neurosci 36:2425–2437. https://doi.org/10.1523/JNEUROSCI.2569-15.2016.
39. Small SA, Kent K, Pierce A, Leung C, Kang MS, Okada H, Honig L, Vonsattel JP, Kim TW. 2005. Model-guided microarray implicates the retromer complex in Alzheimer's disease. Ann Neurol 58:909–919. https://doi.org/10.1002/ana.20667.
40. Muhammad A, Flores I, Zhang H, Yu R, Staniszewski A, Planel E, Herman M, Ho L, Kreber R, Honig LS, Ganetzky B, Duff K, Arancio O, Small SA. 2008. Retromer deficiency observed in Alzheimer's disease causes hippocampal dysfunction, neurodegeneration, and Abeta accumulation. Proc Natl Acad Sci U S A 105:7327–7332. https://doi.org/10.1073/pnas.0802545105.
41. Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinessi L, Rainero I, Sorbi S, Bruni A, Duara R, Friedland RP, Inzelberg R, Hampe W, Bujo H, Song YQ, Andersen OM, Willnow TE, Graff-Radford N, Petersen RC, Dickson D, Der SD, Fraser PE, Schmitt-Ulms G, Younkin S, Mayeux R, Farrer LA, St George-Hyslop P. 2007. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 39:168–177. https://doi.org/10.1038/ng1943.
42. Lane RF, Raines SM, Steele JW, Ehrlich ME, Lah JA, Small SA, Tanzi RE, Attie AD, Gandy S. 2010. Diabetes-associated SorCS1 regulates Alzheimer's amyloid-beta metabolism: evidence for involvement of SorL1 and the retromer complex. J Neurosci 30:13110–13115. https://doi.org/10.1523/JNEUROSCI.3872-10.2010.
43. Reitz C, Cheng R, Rogaeva E, Lee JH, Tokuhiro S, Zou F, Bettens K, Sleegers K, Tan EK, Kimura R, Shibata N, Arai H, Kamboh MI, Prince JA, Maier W, Riemenschneider M, Owen M, Harold D, Hollingworth P, Cellini E, Sorbi S, Nacmias B, Takeda M, Pericak-Vance MA, Haines JL, Younkin S, Williams J, van Broeckhoven C, Farrer LA, St George-Hyslop PH, Mayeux R. 2011. Meta-analysis of the association between variants in SORL1 and Alzheimer disease. Arch Neurol 68:99–106. https://doi.org/10.1001/archneurol.2010.346.
44. Verheijen J, Van den Bossche T, van der Zee J, Engelborghs S, Sanchez-Valle R, Lladó A, Graff C, Thonberg H, Pastor P, Ortega-Cubero S, Pastor MA, Benussi L, Ghidoni R, Binetti G, Clarimon J, Lleó A, Fortea J, de Mendonça A, Martins M, Grau-Rivera O, Gelpi E, Bettens K, Mateiu L, Dillen L, Cras P, De Deyn PP, Van Broeckhoven C, Sleegers K. 2016. A comprehensive study of the genetic impact of rare variants in SORL1 in European early-onset Alzheimer's disease. Acta Neuropathol 132:213–224. https://doi.org/10.1007/s00401-016-1566-9.
45. Thonberg H, Chiang HH, Lilius L, Forsell C, Lindström AK, Johansson C, Björkström J, Thordardottir S, Sleegers K, Van Broeckhoven C, Rönnbäck A, Graff C. 2017. Identification and description of three families with familial Alzheimer disease that segregate variants in the SORL1 gene. Acta Neuropathol Commun 5:43. https://doi.org/10.1186/s40478-017-0441-9.
46. Vardarajan BN, Bruesegem SY, Harbour ME, St George-Hyslop P, Seaman MN, Farrer LA. 2012. Identification of Alzheimer disease-associated variants in genes that regulate retromer function. Neurobiol Aging 33:2231.
47. Cataldo AM, Peterhoff CM, Troncoso JC, Gomez-Isla T, Hyman BT, Nixon RA. 2000. Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. Am J Pathol 157:277–286. https://doi.org/10.1016/s0002-9440(10)64538-5.
48. Cataldo AM, Barnett JL, Pieroni C, Nixon RA. 1997. Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer's disease: neuropathologic evidence for a mechanism of increased beta-amyloidogenesis. J Neurosci 17:6142–6151. https://doi.org/10.1523/JNEUROSCI.17-16-06142.1997.
49. Peric A, Annaert W. 2015. Early etiology of Alzheimer's disease: tipping the balance toward autophagy or endosomal dysfunction? Acta Neuropathol 129:363–381. https://doi.org/10.1007/s00401-014-1379-7.
50. Ye S, Huang Y, Müllendorff K, Dong L, Giedt G, Meng EC, Cohen FE, Kuntz ID, Weisgraber KH, Mahley RW. 2005. Apolipoprotein (apo) E4 enhances amyloid beta peptide production in cultured neuronal cells: apoE structure as a potential therapeutic target. Proc Natl Acad Sci U S A 102:18700–18705. https://doi.org/10.1073/pnas.0508693102.
51. Yu JT, Tan L, Hardy J. 2014. Apolipoprotein E in Alzheimer's disease: an update. Annu Rev Neurosci 37:79–100. https://doi.org/10.1146/annurev-neuro-071013-014300.
52. Zhao N, Liu CC, Van Ingelgom AJ, Martens YA, Linares C, Knight JA, Painter MM, Sullivan PM, Bu G. 2017. Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. Neuron 96:115–129. https://doi.org/10.1016/j.neuron.2017.09.003.
53. Nuriel T, Peng KY, Ashok A, Dillman AA, Figueroa HY, Apuzzo J, Ambat J, Levy E, Cookson MR, Mathews PM, Duff KE. 2017. The endosomal-lysosomal pathway is dysregulated by APOE4 expression in vivo. Front Neurosci 11:702. https://doi.org/10.3389/fnins.2017.00702.
54. Hunn BH, Cragg SJ, Bolam JP, Spillantini MG, Wade-Martins R. 2015. Impaired intracellular trafficking defines early Parkinson's disease. Trends Neurosci 38:178–188. https://doi.org/10.1016/j.tins.2014.12.009.
55. Qureshi YH, Patel VM, Berman DE, Kothiya MJ, Neufeld JL, Vardarajan B, Tang M, Reyes-Dumeyer D, Lantigua R, Medrano M, Jiménez-Velázquez IJ, Small SA, Reitz C. 2018. An Alzheimer's linked loss-of-function CLN5 variant impairs cathepsin D maturation consistent with a retromer trafficking defect. Mol Cell Biol 38:e00011-18. https://doi.org/10.1128/MCB.00011-18.
56. Maruzs T, Lőrincz P, Szatmári Z, Széplaki S, Sándor Z, Lakatos Z, Puska G, Juhász G, Sass M. 2015. Retromer ensures the degradation of autophagic cargo by maintaining lysosome function in Drosophila. Traffic 16:1088–1107. https://doi.org/10.1111/tra.12309.
57. Tammineni P, Jeong YY, Feng T, Aikal D, Cai Q. 2017. Impaired axonal retrograde trafficking of the retromer complex augments lysosomal

deficits in Alzheimer's disease neurons. Hum Mol Genet 26:4352–4366. https://doi.org/10.1093/hmg/ddx321.
58. Cárcel-Trullols J, Kovács AD, Pearce DA. 2015. Cell biology of the NCL proteins: what they do and don't do. Biochim Biophys Acta 1852:2242–2255. https://doi.org/10.1016/j.bbadis.2015.04.027.
59. Haltia M. 2003. The neuronal ceroid-lipofuscinoses. J Neuropathol Exp Neurol 62:1–13. https://doi.org/10.1093/jnen/62.1.1.
60. Haltia M. 2006. The neuronal ceroid-lipofuscinoses: from past to present. Biochim Biophys Acta 1762:850–856. https://doi.org/10.1016/j.bbadis.2006.06.010.
61. Butz ES, Chandrachud U, Mole SE, Cotman SL. 2019. Moving towards a new era of genomics in the neuronal ceroid lipofuscinoses. Biochim Biophys Acta Mol Basis Dis 1866:165571. https://doi.org/10.1016/j.bbadis.2019.165571.
62. Mamo A, Jules F, Dumaresq-Doiron K, Costantino S, Lefrancois S. 2012. The role of ceroid lipofuscinosis neuronal protein 5 (CLN5) in endosomal sorting. Mol Cell Biol 32:1855–1866. https://doi.org/10.1128/MCB.06726-11.
63. Yasa S, Modica G, Sauvageau E, Kaleem A, Hermey G, Lefrancois S. 2020. CLN3 regulates endosomal function by modulating Rab7A-effector interactions. J Cell Sci 133:jcs234047. https://doi.org/10.1242/jcs.234047.
64. Verkruyse LA, Hofmann SL. 1996. Lysosomal targeting of palmitoyl-protein thioesterase. J Biol Chem 271:15831–15836. https://doi.org/10.1074/jbc.271.26.15831.
65. Kornfeld S, Mellman I. 1989. The biogenesis of lysosomes. Annu Rev Cell Biol 5:483–525. https://doi.org/10.1146/annurev.cb.05.110189.002411.
66. Appu AP, Bagh MB, Sadhukhan T, Mondal A, Casey S, Mukherjee AB. 2019. Cln3-mutations underlying juvenile neuronal ceroid lipofuscinosis cause significantly reduced levels of palmitoyl-protein thioesterases-1 (Ppt1)-protein and Ppt1-enzyme activity in the lysosome. J Inherit Metab Dis 42:944–954. https://doi.org/10.1002/jimd.12106.
67. Doccini S, Sartori S, Maeser S, Pezzini F, Rossato S, Moro F, Toldo I, Przybylski M, Santorelli FM, Simonati A. 2016. Early infantile neuronal ceroid lipofuscinosis (CLN10 disease) associated with a novel mutation in CTSD. J Neurol 263:1029–1032. https://doi.org/10.1007/s00415-016-8111-6.
68. Hersheson J, Burke D, Clayton R, Anderson G, Jacques TS, Mills P, Wood NW, Gissen P, Clayton P, Fearnley J, Mole SE, Houlden H. 2014. Cathepsin D deficiency causes juvenile-onset ataxia and distinctive muscle pathology. Neurology 83:1873–1875. https://doi.org/10.1212/WNL.0000000000000981.
69. Liu W, Kleine-Holthaus SM, Herranz-Martin S, Aristorena M, Mole SE, Smith AJ, Ali RR, Rahim AA. 2020. Experimental gene therapies for the NCLs. Biochim Biophys Acta Mol Basis Dis 1866:165772. https://doi.org/10.1016/j.bbadis.2020.165772.
70. Vidoni C, Follo C, Savino M, Melone MA, Isidoro C. 2016. The role of cathepsin D in the pathogenesis of human neurodegenerative disorders. Med Res Rev 36:845–870. https://doi.org/10.1002/med.21394.
71. Benes P, Vetvicka V, Fusek M. 2008. Cathepsin D–many functions of one aspartic protease. Crit Rev Oncol Hematol 68:12–28. https://doi.org/10.1016/j.critrevonc.2008.02.008.
72. Canuel M, Korkidakis A, Konnyu K, Morales CR. 2008. Sortilin mediates the lysosomal targeting of cathepsins D and H. Biochem Biophys Res Commun 373:292–297. https://doi.org/10.1016/j.bbrc.2008.06.021.
73. Stoka V, Turk V, Turk B. 2016. Lysosomal cathepsins and their regulation in aging and neurodegeneration. Ageing Res Rev 32:22–37. https://doi.org/10.1016/j.arr.2016.04.010.
74. von Figura K, Hasilik A. 1986. Lysosomal enzymes and their receptors. Annu Rev Biochem 55:167–193. https://doi.org/10.1146/annurev.bi.55.070186.001123.
75. Coutinho MF, Lacerda L, Pinto E, Ribeiro H, Macedo-Ribeiro S, Castro L, Prata MJ, Alves S. 2015. Molecular and computational analyses of genes involved in mannose 6-phosphate independent trafficking. Clin Genet 88:190–194. https://doi.org/10.1111/cge.12469.
76. Chai YL, Chong JR, Weng J, Howlett D, Halsey A, Lee JH, Attems J, Aarsland D, Francis PT, Chen CP, Lai M. 2019. Lysosomal cathepsin D is upregulated in Alzheimer's disease neocortex and may be a marker for neurofibrillary degeneration. Brain Pathol 29:63–74. https://doi.org/10.1111/bpa.12631.
77. Cataldo AM, Paskevich PA, Kominami E, Nixon RA. 1991. Lysosomal hydrolases of different classes are abnormally distributed in brains of patients with Alzheimer disease. Proc Natl Acad Sci U S A 88:10998–11002. https://doi.org/10.1073/pnas.88.24.10998.
78. Rojas R, van Vlijmen T, Mardones GA, Prabhu Y, Rojas AL, Mohammed S, Heck AJ, Raposo G, van der Sluijs P, Bonifacino JS. 2008. Regulation of retromer recruitment to endosomes by sequential action of Rab5 and Rab7. J Cell Biol 183:513–526. https://doi.org/10.1083/jcb.200804048.
79. Khurana V, Elson-Schwab I, Fulga TA, Sharp KA, Loewen CA, Mulkearns E, Tyynela J, Scherzer CR, Feany MB. 2010. Lysosomal dysfunction promotes cleavage and neurotoxicity of tau in vivo. PLoS Genet 6:e1001026. https://doi.org/10.1371/journal.pgen.1001026.
80. Kenessey A, Nacharaju P, Ko LW, Yen SH. 1997. Degradation of tau by lysosomal enzyme cathepsin D: implication for Alzheimer neurofibrillary degeneration. J Neurochem 69:2026–2038. https://doi.org/10.1046/j.1471-4159.1997.69052026.x.
81. Zhang QY, Tan MS, Yu JT, Tan L. 2016. The role of retromer in Alzheimer's disease. Mol Neurobiol 53:4201–4209. https://doi.org/10.1007/s12035-015-9366-0.
82. Mirza M, Vainshtein A, DiRonza A, Chandrachud U, Haslett LJ, Palmieri M, Storch S, Groh J, Dobzinski N, Napolitano G, Schmidtke C, Kerkovich DM. 2019. The CLN3 gene and protein: what we know. Mol Genet Genomic Med 7:e859. https://doi.org/10.1002/mgg3.859.
83. Kuper WFE, van Alfen C, Rigterink RH, Fuchs SA, van Genderen MM, van Hasselt PM. 2018. Timing of cognitive decline in CLN3 disease. J Inherit Metab Dis 41:257–261. https://doi.org/10.1007/s10545-018-0143-x.
84. Ouseph MM, Kleinman ME, Wang QJ. 2016. Vision loss in juvenile neuronal ceroid lipofuscinosis (CLN3 disease). Ann N Y Acad Sci 1371:55–67. https://doi.org/10.1111/nyas.12990.
85. Phillips SN, Benedict JW, Weimer JM, Pearce DA. 2005. CLN3, the protein associated with batten disease: structure, function and localization. J Neurosci Res 79:573–583. https://doi.org/10.1002/jnr.20367.
86. Ramirez-Montealegre D, Pearce DA. 2005. Defective lysosomal arginine transport in juvenile Batten disease. Hum Mol Genet 14:3759–3773. https://doi.org/10.1093/hmg/ddi406.
87. Kama R, Kanneganti V, Ungermann C, Gerst JE. 2011. The yeast Batten disease orthologue Btn1 controls endosome–Golgi retrograde transport via SNARE assembly. J Cell Biol 195:203–215. https://doi.org/10.1083/jcb.201102115.
88. Metcalf DJ, Calvi AA, Seaman MN, Mitchison HM, Cutler DF. 2008. Loss of the Batten disease gene CLN3 prevents exit from the TGN of the mannose 6-phosphate receptor. Traffic 9:1905–1914. https://doi.org/10.1111/j.1600-0854.2008.00807.x.
89. Narayan SB, Rakheja D, Tan L, Pastor JV, Bennett MJ. 2006. CLN3P, the Batten's disease protein, is a novel palmitoyl-protein Delta-9 desaturase. Ann Neurol 60:570–577. https://doi.org/10.1002/ana.20975.
90. Seaman MN, Harbour ME, Tattersall D, Read E, Bright N. 2009. Membrane recruitment of the cargo-selective retromer subcomplex is catalysed by the small GTPase Rab7 and inhibited by the Rab-GAP TBC1D5. J Cell Sci 122:2371–2382. https://doi.org/10.1242/jcs.048686.
91. Nakamura S, Yoshimori T. 2017. New insights into autophagosome-lysosome fusion. J Cell Sci 130:1209–1216. https://doi.org/10.1242/jcs.196352.
92. Jimenez-Orgaz A, Kvainickas A, Nagele H, Denner J, Eimer S, Dengjel J, Steinberg F. 2018. Control of RAB7 activity and localization through the retromer-TBC1D5 complex enables RAB7-dependent mitophagy. EMBO J 37:235–254. https://doi.org/10.15252/embj.201797128.
93. Holmberg V, Jalanko A, Isosomppi J, Fabritius AL, Peltonen L, Kopra O. 2004. The mouse ortholog of the neuronal ceroid lipofuscinosis CLN5 gene encodes a soluble lysosomal glycoprotein expressed in the developing brain. Neurobiol Dis 16:29–40. https://doi.org/10.1016/j.nbd.2003.12.019.
94. Schmiedt ML, Blom T, Blom T, Kopra O, Wong A, von Schantz-Fant C, Ikonen E, Kuronen M, Jauhiainen M, Cooper JD, Jalanko A. 2012. Cln5-deficiency in mice leads to microglial activation, defective myelination and changes in lipid metabolism. Neurobiol Dis 46:19–29. https://doi.org/10.1016/j.nbd.2011.12.009.
95. Moharir A, Peck SH, Budden T, Lee SY. 2013. The role of N-glycosylation in folding, trafficking, and functionality of lysosomal protein CLN5. PLoS One 8:e74299. https://doi.org/10.1371/journal.pone.0074299.
96. Silva B, Adams J, Lee SY. 2015. Proteolytic processing of the neuronal ceroid lipofuscinosis related lysosomal protein CLN5. Exp Cell Res 338:45–53. https://doi.org/10.1016/j.yexcr.2015.08.021.
97. Lebrun AH, Storch S, Ruschendorf F, Schmiedt ML, Kyttala A, Mole SE, Kitzmuller C, Saar K, Mewasingh LD, Boda V, Kohlschutter A, Ullrich K, Braulke T, Schulz A. 2009. Retention of lysosomal protein CLN5 in the endoplasmic reticulum causes neuronal ceroid lipofuscinosis in Asian sibship. Hum Mutat 30:E651–E661. https://doi.org/10.1002/humu.21010.

98. Isosomppi J, Vesa J, Jalanko A, Peltonen L. 2002. Lysosomal localization of the neuronal ceroid lipofuscinosis CLN5 protein. Hum Mol Genet 11:885–891. https://doi.org/10.1093/hmg/11.8.885.
99. Vesa J, Chin MH, Oelgeschlager K, Isosomppi J, DellAngelica EC, Jalanko A, Peltonen L. 2002. Neuronal ceroid lipofuscinoses are connected at molecular level: interaction of CLN5 protein with CLN2 and CLN3. Mol Biol Cell 13:2410–2420. https://doi.org/10.1091/mbc.e02-01-0031.
100. Miura E, Hasegawa T, Konno M, Suzuki M, Sugeno N, Fujikake N, Geisler S, Tabuchi M, Oshima R, Kikuchi A, Baba T, Wada K, Nagai Y, Takeda A, Aoki M. 2014. VPS35 dysfunction impairs lysosomal degradation of alpha-synuclein and exacerbates neurotoxicity in a Drosophila model of Parkinson's disease. Neurobiol Dis 71:1–13. https://doi.org/10.1016/j.nbd.2014.07.014.
101. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N, Deng S, Liddelow SA, Zhang C, Daneman R, Maniatis T, Barres BA, Wu JQ. 2014. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci 34:11929–11947. https://doi.org/10.1523/JNEUROSCI.1860-14.2014.
102. Ulland TK, Song WM, Huang SC, Ulrich JD, Sergushichev A, Beatty WL, Loboda AA, Zhou Y, Cairns NJ, Kambal A, Loginicheva E, Gilfillan S, Cella M, Virgin HW, Unanue ER, Wang Y, Artyomov MN, Holtzman DM, Colonna M. 2017. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell 170:649–663. https://doi.org/10.1016/j.cell.2017.07.023.
103. Lucin KM, O'Brien CE, Bieri G, Czirr E, Mosher KI, Abbey RJ, Mastroeni DF, Rogers J, Spencer B, Masliah E, Wyss-Coray T. 2013. Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. Neuron 79:873–886. https://doi.org/10.1016/j.neuron.2013.06.046.
104. Nita DA, Mole SE, Minassian BA. 2016. Neuronal ceroid lipofuscinoses. Epileptic Disord 18:73–88. https://doi.org/10.1684/epd.2016.0844.
105. Aladeokin AC, Akiyama T, Kimura A, Kimura Y, Takahashi-Jitsuki A, Nakamura H, Makihara H, Masukawa D, Nakabayashi J, Hirano H, Nakamura F, Saito T, Saido T, Goshima Y. 2019. Network-guided analysis of hippocampal proteome identifies novel proteins that colocalize with Abeta in a mice model of early-stage Alzheimer's disease. Neurobiol Dis 132:104603. https://doi.org/10.1016/j.nbd.2019.104603.
106. Koster KP, Yoshii A. 2019. Depalmitoylation by palmitoyl-protein thioesterase 1 in neuronal health and degeneration. Front Synaptic Neurosci 11:25. https://doi.org/10.3389/fnsyn.2019.00025.
107. Cho E, Park M. 2016. Palmitoylation in Alzheimer's disease and other neurodegenerative diseases. Pharmacol Res 111:133–151. https://doi.org/10.1016/j.phrs.2016.06.008.
108. Zaręba-Kozioł M, Figiel I, Bartkowiak-Kaczmarek A, Włodarczyk J. 2018. Insights into protein S-palmitoylation in synaptic plasticity and neurological disorders: potential and limitations of methods for detection and analysis. Front Mol Neurosci 11:175. https://doi.org/10.3389/fnmol.2018.00175.
109. Ahtiainen L, Luiro K, Kauppi M, Tyynelä J, Kopra O, Jalanko A. 2006. Palmitoyl protein thioesterase 1 (PPT1) deficiency causes endocytic defects connected to abnormal saposin processing. Exp Cell Res 312:1540–1553. https://doi.org/10.1016/j.yexcr.2006.01.034.
110. Johnson TB, Cain JT, White KA, Ramirez-Montealegre D, Pearce DA, Weimer JM. 2019. Therapeutic landscape for Batten disease: current treatments and future prospects. Nat Rev Neurol 15:161–178. https://doi.org/10.1038/s41582-019-0138-8.
111. Kim SJ, Zhang Z, Sarkar C, Tsai PC, Lee YC, Dye L, Mukherjee AB. 2008. Palmitoyl protein thioesterase-1 deficiency impairs synaptic vesicle recycling at nerve terminals, contributing to neuropathology in humans and mice. J Clin Invest 118:3075–3086. https://doi.org/10.1172/JCI33482.
112. Kielar C, Wishart TM, Palmer A, Dihanich S, Wong AM, Macauley SL, Chan CH, Sands MS, Pearce DA, Cooper JD, Gillingwater TH. 2009. Molecular correlates of axonal and synaptic pathology in mouse models of Batten disease. Hum Mol Genet 18:4066–4080. https://doi.org/10.1093/hmg/ddp355.
113. Rambaran RN, Serpell LC. 2008. Amyloid fibrils: abnormal protein assembly. Prion 2:112–117. https://doi.org/10.4161/pri.2.3.7488.
114. Sengupta U, Nilson AN, Kayed R. 2016. The role of amyloid-beta oligomers in toxicity, propagation, and immunotherapy. EBioMedicine 6:42–49. https://doi.org/10.1016/j.ebiom.2016.03.035.
115. Sole-Domenech S, Rojas AV, Maisuradze GG, Scheraga HA, Lobel P, Maxfield FR. 2018. Lysosomal enzyme tripeptidyl peptidase 1 destabilizes fibrillar Abeta by multiple endoproteolytic cleavages within the beta-sheet domain. Proc Natl Acad Sci U S A 115:1493–1498. https://doi.org/10.1073/pnas.1719808115.
116. Minami SS, Min SW, Krabbe G, Wang C, Zhou Y, Asgarov R, Li Y, Martens LH, Elia LP, Ward ME, Mucke L, Farese RV, Jr, Gan L. 2014. Progranulin protects against amyloid beta deposition and toxicity in Alzheimer's disease mouse models. Nat Med 20:1157–1164. https://doi.org/10.1038/nm.3672.
117. Fenoglio C, Galimberti D, Cortini F, Kauwe JS, Cruchaga C, Venturelli E, Villa C, Serpente M, Scalabrini D, Mayo K, Piccio LM, Clerici F, Albani D, Mariani C, Forloni G, Bresolin N, Goate AM, Scarpini E. 2009. Rs5848 variant influences GRN mRNA levels in brain and peripheral mononuclear cells in patients with Alzheimer's disease. J Alzheimers Dis 18:603–612. https://doi.org/10.3233/JAD-2009-1170.
118. Satoh J-I, Kino Y, Kawana N, Yamamoto Y, Ishida T, Saito Y, Arima K. 2014. TMEM106B expression is reduced in Alzheimer's disease brains. Alzheimers Res Ther 6:17. https://doi.org/10.1186/alzrt247.
119. Pereson S, Wils H, Kleinberger G, McGowan E, Vandewoestyne M, Van Broeck B, Joris G, Cuijt I, Deforce D, Hutton M, Van Broeckhoven C, Kumar-Singh S. 2009. Progranulin expression correlates with dense-core amyloid plaque burden in Alzheimer disease mouse models. J Pathol 219:173–181. https://doi.org/10.1002/path.2580.
120. Takahashi H, Klein ZA, Bhagat SM, Kaufman AC, Kostylev MA, Ikezu T, Strittmatter SM, Alzheimer's Disease Neuroimaging Initiative. 2017. Opposing effects of progranulin deficiency on amyloid and tau pathologies via microglial TYROBP network. Acta Neuropathol 133:785–807. https://doi.org/10.1007/s00401-017-1668-z.
121. Hosokawa M, Arai T, Masuda-Suzukake M, Kondo H, Matsuwaki T, Nishihara M, Hasegawa M, Akiyama H. 2015. Progranulin reduction is associated with increased tau phosphorylation in P301L tau transgenic mice. J Neuropathol Exp Neurol 74:158–165. https://doi.org/10.1097/NEN.0000000000000158.
122. Arrant AE, Onyilo VC, Unger DE, Roberson ED. 2018. Progranulin gene therapy improves lysosomal dysfunction and microglial pathology associated with frontotemporal dementia and neuronal ceroid lipofuscinosis. J Neurosci 38:2341–2358. https://doi.org/10.1523/JNEUROSCI.3081-17.2018.
123. Mendsaikhan A, Tooyama I, Walker DG. 2019. Microglial progranulin: involvement in Alzheimer's disease and neurodegenerative diseases. Cells 8:230. https://doi.org/10.3390/cells8030230.
124. Lui H, Zhang J, Makinson SR, Cahill MK, Kelley KW, Huang HY, Shang Y, Oldham MC, Martens LH, Gao F, Coppola G, Sloan SA, Hsieh CL, Kim CC, Bigio EH, Weintraub S, Mesulam MM, Rademakers R, Mackenzie IR, Seeley WW, Karydas A, Miller BL, Borroni B, Ghidoni R, Farese RV, Jr, Paz JT, Barres BA, Huang EJ. 2016. Progranulin deficiency promotes circuit-specific synaptic pruning by microglia via complement activation. Cell 165:921–935. https://doi.org/10.1016/j.cell.2016.04.001.
125. Petkau TL, Kosior N, de Asis K, Connolly C, Leavitt BR. 2017. Selective depletion of microglial progranulin in mice is not sufficient to cause neuronal ceroid lipofuscinosis or neuroinflammation. J Neuroinflamm 14:225. https://doi.org/10.1186/s12974-017-1000-9.
126. Smith KR, Dahl HH, Canafoglia L, Andermann E, Damiano J, Morbin M, Bruni AC, Giaccone G, Cossette P, Saftig P, Grotzinger J, Schwake M, Andermann F, Staropoli JF, Sims KB, Mole SE, Franceschetti S, Alexander NA, Cooper JD, Chapman HA, Carpenter S, Berkovic SF, Bahlo M. 2013. Cathepsin F mutations cause type B Kufs disease, an adult-onset neuronal ceroid lipofuscinosis. Hum Mol Genet 22:1417–1423. https://doi.org/10.1093/hmg/dds558.
127. Berkovic SF, Oliver KL, Canafoglia L, Krieger P, Damiano JA, Hildebrand MS, Morbin M, Vears DF, Sofia V, Giuliano L, Garavaglia B, Simonati A, Santorelli FM, Gambardella A, Labate A, Belcastro V, Castellotti B, Ozkara C, Zeman A, Rankin J, Mole SE, Aguglia U, Farrell M, Rajagopalan S, McDougall A, Brammah S, Andermann F, Andermann E, Dahl HM, Franceschetti S, Carpenter S. 2019. Kufs disease due to mutation of CLN6: clinical, pathological and molecular genetic features. Brain 142:59–69. https://doi.org/10.1093/brain/awy297.
128. Di Fabio R, Moro F, Pestillo L, Meschini MC, Pezzini F, Doccini S, Casali C, Pierelli F, Simonati A, Santorelli FM. 2014. Pseudo-dominant inheritance of a novel CTSF mutation associated with type B Kufs disease. Neurology 83:1769–1770. https://doi.org/10.1212/WNL.0000000000000953.
129. Peters J, Rittger A, Weisner R, Knabbe J, Zunke F, Rothaug M, Damme M, Berkovic SF, Blanz J, Saftig P, Schwake M. 2015. Lysosomal integral membrane protein type-2 (LIMP-2/SCARB2) is a substrate of cathepsin-F, a cysteine protease mutated in type-B-Kufs-disease.

Biochem Biophys Res Commun 457:334–340. https://doi.org/10.1016/j.bbrc.2014.12.111.
130. Bras J, Djaldetti R, Alves AM, Mead S, Darwent L, Lleo A, Molinuevo JL, Blesa R, Singleton A, Hardy J, Clarimon J, Guerreiro R. 2016. Exome sequencing in a consanguineous family clinically diagnosed with early-onset Alzheimer's disease identifies a homozygous CTSF mutation. Neurobiol Aging 46:236–241.
131. Dolzhanskaya N, Gonzalez MA, Sperziani F, Stefl S, Messing J, Wen GY, Alexov E, Zuchner S, Velinov M. 2014. A novel p.Leu(381)Phe mutation in presenilin 1 is associated with very early onset and unusually fast progressing dementia as well as lysosomal inclusions typically seen in Kufs disease. J Alzheimers Dis 39:23–27. https://doi.org/10.3233/JAD-131340.
132. Zhang Y, Sloan SA, Clarke LE, Caneda C, Plaza CA, Blumenthal PD, Vogel H, Steinberg GK, Edwards MS, Li G, Duncan JA, III, Cheshier SH, Shuer LM, Chang EF, Grant GA, Gephart MG, Barres BA. 2016. Purification and characterization of progenitor and mature human astrocytes reveals transcriptional and functional differences with mouse. Neuron 89:37–53. https://doi.org/10.1016/j.neuron.2015.11.013.
133. Qureshi YH, Berman DE, Klein RL, Patel VM, Simoes S, Kannan S, Cox R, Waksal SD, Stevens B, Petsko GA, Small SA. 2019. Retromer repletion with AAV9-VPS35 restores endosomal function in the mouse hippocampus. bioRxiv https://doi.org/10.1101/618496.
134. Berman DE, Ringe D, Petsko GA, Small SA. 2015. The use of pharmacological retromer chaperones in Alzheimer's disease and other endosomal-related disorders. Neurotherapeutics 12:12–18. https://doi.org/10.1007/s13311-014-0321-y.
135. Young JE, Fong LK, Frankowski H, Petsko GA, Small SA, Goldstein L. 2018. Stabilizing the retromer complex in a human stem cell model of Alzheimer's disease reduces TAU phosphorylation independently of amyloid precursor protein. Stem Cell Rep 10:1046–1058. https://doi.org/10.1016/j.stemcr.2018.01.031.
136. Mecozzi VJ, Berman DE, Simoes S, Vetanovetz C, Awal MR, Patel VM, Schneider RT, Petsko GA, Ringe D, Small SA. 2014. Pharmacological chaperones stabilize retromer to limit APP processing. Nat Chem Biol 10:443–449. https://doi.org/10.1038/nchembio.1508.
137. Sapir T, Segal M, Grigoryan G, Hansson KM, James P, Segal M, Reiner O. 2019. The interactome of palmitoyl-protein thioesterase 1 (PPT1) affects neuronal morphology and function. Front Cell Neurosci 13:92. https://doi.org/10.3389/fncel.2019.00092.
138. Camp LA, Hofmann SL. 1993. Purification and properties of a palmitoyl-protein thioesterase that cleaves palmitate from H-Ras. J Biol Chem 268:22566–22574.
139. Lin L, Sohar I, Lackland H, Lobel P. 2001. The human CLN2 protein/tripeptidyl-peptidase I is a serine protease that autoactivates at acidic pH. J Biol Chem 276:2249–2255. https://doi.org/10.1074/jbc.M008562200.
140. Rawlings ND, Barrett AJ. 1999. Tripeptidyl-peptidase I is apparently the CLN2 protein absent in classical late-infantile neuronal ceroid lipofuscinosis. Biochim Biophys Acta 1429:496–500. https://doi.org/10.1016/s0167-4838(98)00238-6.
141. Ezaki J, Takeda-Ezaki M, Oda K, Kominami E. 2000. Characterization of endopeptidase activity of tripeptidyl peptidase-I/CLN2 protein which is deficient in classical late infantile neuronal ceroid lipofuscinosis. Biochem Biophys Res Commun 268:904–908. https://doi.org/10.1006/bbrc.2000.2207.
142. Sindelar M, Dyke JP, Deeb RS, Sondhi D, Kaminsky SM, Kosofsky BE, Ballon DJ, Crystal RG, Gross SS. 2018. Untargeted metabolite profiling of cerebrospinal fluid uncovers biomarkers for severity of late infantile neuronal ceroid lipofuscinosis (CLN2, Batten disease). Sci Rep 8:15229. https://doi.org/10.1038/s41598-018-33449-0.
143. Zhang H, Kelley WL, Chamberlain LH, Burgoyne RD, Wollheim CB, Lang J. 1998. Cysteine-string proteins regulate exocytosis of insulin independent from transmembrane ion fluxes. FEBS Lett 437:267–272. https://doi.org/10.1016/s0014-5793(98)01233-2.
144. Chamberlain LH, Burgoyne RD. 2000. Cysteine-string protein: the chaperone at the synapse. J Neurochem 74:1781–1789. https://doi.org/10.1046/j.1471-4159.2000.0741781.x.
145. Chamberlain LH, Burgoyne RD. 1998. Cysteine string protein functions directly in regulated exocytosis. Mol Biol Cell 9:2259–2267. https://doi.org/10.1091/mbc.9.8.2259.
146. Greaves J, Lemonidis K, Gorleku OA, Cruchaga C, Grefen C, Chamberlain LH. 2012. Palmitoylation-induced aggregation of cysteine-string protein mutants that cause neuronal ceroid lipofuscinosis. J Biol Chem 287:37330–37339. https://doi.org/10.1074/jbc.M112.389098.
147. Huber RJ, Mathavarajah S. 2018. Secretion and function of Cln5 during the early stages of Dictyostelium development. Biochim Biophys Acta Mol Cell Res 1865:1437–1450. https://doi.org/10.1016/j.bbamcr.2018.07.017.
148. Huber RJ, Mathavarajah S. 2018. Cln5 is secreted and functions as a glycoside hydrolase in Dictyostelium. Cell Signal 42:236–248. https://doi.org/10.1016/j.cellsig.2017.11.001.
149. Singh Y, Leinonen H, Fazaludeen F, Jaronen M, Guest D, Buckley N, Byts N, Oksa P, Jalkanen K, Iqbal I, Huuskonen M, Savchenko E, Keksa-Goldsteine V, Chew S, Myllyharju J, Tanila H, Ooi L, Koistinaho J, Kanninen KM, Malm T. 2019. Loss of Cln5 leads to altered Gad1 expression and deficits in interneuron development in mice. Hum Mol Genet 28:3309–3322. https://doi.org/10.1093/hmg/ddz165.
150. Doccini S, Morani F, Nesti C, Pezzini F, Calza G, Soliymani R, Signore G, Rocchiccioli S, Kanninen KM, Huuskonen MT, Baumann MH, Simonati A, Lalowski MM, Santorelli FM. 2020. Proteomic and functional analyses in disease models reveal CLN5 protein involvement in mitochondrial dysfunction. Cell Death Discov 6:18. https://doi.org/10.1038/s41420-020-0250-y.
151. Adams J, Feuerborn M, Molina JA, Wilden AR, Adhikari B, Budden T, Lee SY. 2019. Autophagy-lysosome pathway alterations and alpha-synuclein up-regulation in the subtype of neuronal ceroid lipofuscinosis, CLN5 disease. Sci Rep 9:151. https://doi.org/10.1038/s41598-018-36379-z.
152. Yamashita A, Shiro Y, Hiraki Y, Yujiri T, Yamazaki T. 2020. Implications of graded reductions in CLN6's anti-aggregate activity for the development of the neuronal ceroid lipofuscinoses. Biochem Biophys Res Commun 525:883–888. https://doi.org/10.1016/j.bbrc.2020.03.019.
153. Kao AW, McKay A, Singh PP, Brunet A, Huang EJ. 2017. Progranulin, lysosomal regulation and neurodegenerative disease. Nat Rev Neurosci 18:325–333. https://doi.org/10.1038/nrn.2017.36.