Moving towards a new era of genomics in the neuronal ceroid lipofuscinoses

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ABSTRACT

The neuronal ceroid lipofuscinoses (NCL) are a group of disorders defined by shared clinical and pathological features, including seizures and progressive decline in vision, neurocognition, and motor functioning, as well as accumulation of autofluorescent lysosomal storage material, or 'ceroid lipofuscin'. Research has revealed thirteen distinct genetic subtypes. Precisely how the gene mutations lead to the clinical phenotype is still incompletely understood, but recent research progress is starting to shed light on disease mechanisms, in both gene-specific and shared pathways. As the application of new sequencing technologies to genetic disease diagnosis has grown, so too has the spectrum of clinical phenotypes caused by mutations in the NCL genes. Most genes causing NCL have probably been identified, underscoring the need for a shift towards applying genomics approaches to achieve a deeper understanding of the molecular basis of the NCLs and related disorders. Here, we summarize the current understanding of the thirteen identified NCL genes and the proteins they encode, touching upon the spectrum of clinical manifestations linked to each of the genes, and we highlight recent progress leading to a broader understanding of key pathways involved in NCL disease pathogenesis and commonalities with other neurodegenerative diseases.

KEYWORDS

NCL GENETICS

The first reports of neuronal ceroid lipofuscinoses (NCL) were in 1826 by Stengel, who (in Norwegian) described 4 siblings with vision loss, a progressive decline in cognitive abilities, loss of speech, seizures, and premature death[1], and in 1903 by Batten, who described cerebral and macular degeneration in two siblings[2]. The term NCL to refer to the group of inherited disorders with the clinical features of vision loss, seizures, and a deterioration of motor and cognitive functioning, along with the presence of ceroid lipofuscin storage material in lysosomes, was suggested in 1969 by Zeman and Dyken[3]. It took many more years for the genetic basis of NCL disorders to be uncovered. The first NCL genes were identified in 1995 [4, 5], and over the course of two and a half decades, a total of thirteen different NCL genes have been identified. The identification of the NCL genes has been reviewed previously [6] and is summarized in Figure 1. This progress was made possible by new technologies arising out of the Human Genome Mapping Project. It led to a shift in NCL disorder classification, which historically had followed broad age-of-onset and assumed the existence of four genes (infantile, late-infantile, juvenile, and adult onset forms of NCL), but now follows a gene-based nomenclature [7]. While most patients with a particular genetic sub-type of NCL show onset of symptoms within the classically defined age window, there are steadily increasing numbers of patients that show variable disease progression and age-of-onset, and a number of variant types are now recognized. Table 1 provides a summary of the thirteen different genetic forms of NCL, the genes identified and the proteins they encode. In most cases, NCL arises due to Mendelian inheritance in an autosomal recessive fashion, except in the case of CLN4 disease, which is inherited in an autosomal dominant pattern. Uniparental disomy has also been observed to give rise to NCL in rare occurrences (e.g. [8-10]).
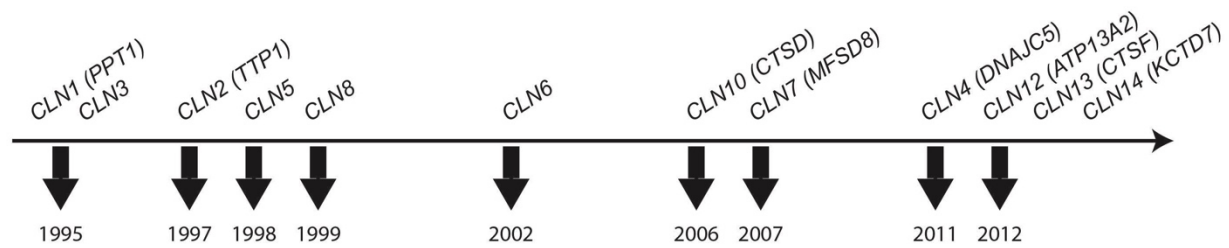
Figure 1: Timeline summarizing the identification of genes causative for NCL diseases (CLN1 – CLN14)

NCL GENES AND THE PROTEINS THEY ENCODE

Consistent with the prominent lysosomal pathology that is a hallmark of the NCL disorders, the early biochemical and gene discoveries clearly highlighted a set of lysosome-localized proteins that were defective in NCL [4, 5, 11]. However, as efforts to fully define the molecular basis of NCL disorders have progressed, it has become evident that some NCL genes encode proteins localized to other, non-lysosomal cellular compartments[12-14], and even that the lysosomal proteins are sometimes found in other organelles, such as synaptic vesicles in neurons (e.g. [15]). Research surrounding the function of the NCL-related proteins has been extensively reviewed elsewhere [16-18]. Here, we will briefly summarize what is known about the function of the NCL related proteins and highlight several of the most recent studies which establish a more in-depth understanding of NCL protein function and the interconnecting pathways (for a pictoral summary, see Figure 2). For additional discussion on emerging common pathways in the NCL disorders, see the recent review by Kline et al in this Special Issue [19].
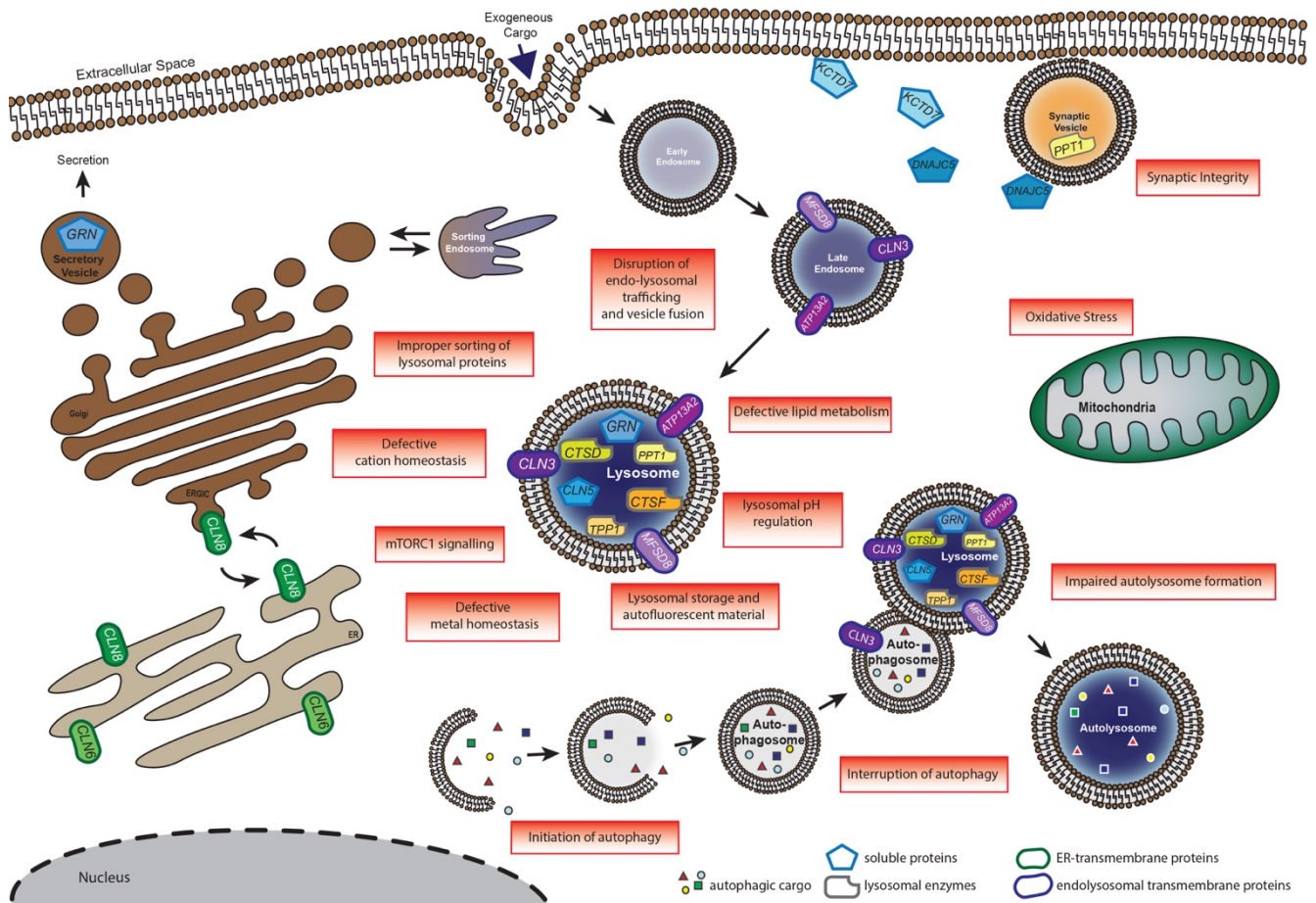
Figure 2: The subcellular pathways of the NCL proteins

The cartoon illustrates the subcellular localization of NCL proteins and highlights the most prominent cellular deficits associated with NCL (red boxes). Although the primary function of most of the NCL proteins is still unknown, it is likely that some function in common pathways converging on autophagy and the lysosome. An overview about the current understanding of NCL proteins' function and recently published literature is given in the main text. ER=Endoplasmic Reticulum; ERGIC=ER-Golgi Intermediate Compartment

Primary lysosomal enzyme deficiencies in CLN1, CLN2, CLN10, and CLN13 disease:

PPT1- CLN1 disease is due to mutations in the *PPT1* gene, encoding palmitoyl-protein thioesterase 1 (PPT1) [4], which catalyzes the removal of palmitate residues from S-acylated, or palmitoylated, proteins [20, 21]. Palmitoylation occurs post-translationally and involves the covalent attachment of fatty acids primarily to cysteine residues. The dynamic process of palmitoylation-depalmitoylation is an important regulatory mechanism for protein stability [22] as well as for many other cellular processes including protein sorting, G-protein signaling and postsynaptic plasticity [23]. Lysosomal PPT1 is suggested to be particularly responsible for depalmitoylation of proteins during protein degradation [22]. Accordingly, CLN1-associated mutations, which result in a reduced or even absent enzyme activity, favor the accumulation of undigested proteins and eventually lead to storage material. However, *in vivo* substrates of PPT1 are largely unknown. Interestingly, the co-chaperone cysteine-string protein alpha (CSPα), another NCL protein, which is encoded by the *DNAJC5* gene (CLN4), has recently been identified as a likely PPT1 substrate [24]. Henderson et al. reported that CLN4-associated mutations in the palmitoylated cysteine string domain of CSPα lead to increased PPT1 burden and PPT1 mislocalization in patient brain, which was accompanied by reduced PPT1 enzyme activity, strongly suggesting a common pathway in the etiology of CLN1 and CLN4 disease [24].

In neurons, PPT1 is also present in axonal and presynaptic compartments at the nerve terminals [25, 26], and several reports indicate a role for PPT1 in maintaining the synaptic pool by regulation of endo- and exocytosis and synaptic vesicle recycling, impacting neurotransmission [25, 27]. Intriguingly, an elevated PPT1 activity has recently been associated with schizophrenia [28]. Palmitoylation and depalmitoylation cycles play an important role in homeostatic plasticity [29], and many synaptic and synaptic vesicle proteins, like CSPα, undergo palmitoylation, including postsynaptic density 95 (PSD95), and several subunits of the AMPA and NMDA receptors (AMPAR and NMDAR, respectively) [30]. A recent

study showed that dendritic spine morphology and the composition of NMDAR subunits was altered in Ppt1-deficient mice, resulting in hyperactivity and aberrant NMDAR currents. This was caused by a hyperpalmitoylation of the NMDAR subunit and could be partially rescued by palmitoylation inhibitors [31]. Furthermore, a recent interactome study of PPT1 revealed interactions with V-type ATPases, voltage-gated calcium channels, and cytoskeletal proteins, in line with the observed morphological and electrophysiological alterations in primary hippocampal neurons isolated from $Ppt1^{-/-}$ mice in the same study [32]. Together, these findings highlight the important emerging role of PPT1 in neuronal-specific subcellular compartments, which is likely to play a role in the severe neurological seizures that are a prominent feature of CLN1 disease [33]. Moreover, consistent with a potential interaction of PPT1 with V-type ATPases, loss of PPT1 activity was shown to interrupt sorting of the V-ATPase, V0a1 subunit, which requires S-palmitoylation for routing to the lysosome. V-ATPase regulates lysosomal acidification, and its mis-sorting led to an elevated lysosomal pH in cells from $Ppt1^{-/-}$ mice, which would be deleterious for lysosomal enzymes that require acidic conditions for proper function and may contribute to further decline in lysosomal function [34].

TPP1- Mutations in *TPP1*, which encodes tripeptidyl-peptidase 1 (TPP1), cause CLN2 disease [11]. TPP1 is a serine protease, and under low pH conditions, TPP1 cleaves tripeptides from the amino terminus of proteins [35]. The crystal structure of proTPP1 and its maturation process under acidifying conditions have been derived [35, 36]. Importantly, although TPP1 function as a serine protease is known, the endogenous substrates for TPP1 are not yet well defined. The 2015 review article by Cárcel-Trullols summarizes candidate TPP1 substrates that have been proposed based on *in vitro* binding interactions and cleavage studies [16]. These include several peptide hormones and the mitochondrial ATP synthase subunit c; whether all of the candidates are endogenous biological substrates requires further study, as most have only been studied *in vitro*. A greater understanding of TPP1 and its biological pathways would

lead to advancement in developing additional treatment approaches for CLN2 disease, which has seen great progress in enzyme replacement and gene therapy approaches [37-40].

CTSD- Mutations in *CTSD*, which encodes cathepsin D, a lysosomal aspartic protease, are known to underlie autosomal recessive congenital NCL, classified as CLN10 disease [41]. Cathepsin D is well known to be important for autophagy and apoptosis, and variation in function of cathepsin D likely plays a role in several neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease [16, 42-46]. Like TPP1, the full catalog of cathepsin D substrates is not known, but a number of neurodegenerative disease-related proteins require cathepsin D for their turnover, like huntingtin [47], α-synuclein[48], and amyloid precursor protein[49]. Interestingly, a recent study has demonstrated that cathepsin D localizes to presynaptic endosomes of GABA synapses and that absence of cathepsin D impairs the biogenesis and synaptic transmission in GABAergic neurons, which may underlie the hyperactivity and seizures observed in *Ctsd*$^{-/-}$ mice [50]. There are increasing reports that alterations in cathepsin D transport and processing occur in several forms of NCL, suggesting cathepsin D regulation may be at least one link in the disease mechanisms across different NCLs (e.g. [51-54]).

CTSF- The *CTSF* gene encodes cathepsin F. *CTSF* mutations were found to be responsible for a rare form of adult onset NCL, classified as CLN13[55]. Cathepsin F is a lysosomal cysteine protease. Recent studies have implicated cathepsin F in regulating endosomal and lysosomal trafficking through a newly defined role in cleavage of the lysosomal integral membrane protein type-2 (LIMP-2), which is a mannose-6-phosphate-independent receptor for lysosomal targeted protein transport[56-58]. Importantly, NCL disease mutations in cathepsin F prevented LIMP-2 processing [56]. Additional endogenous substrates for cathepsin F have yet to be identified.

Soluble lysosomal proteins in CLN5 and CLN11 disease:

CLN5- Although it was initially thought CLN5 may be a transmembrane protein [59], it was subsequently shown that it can exist as a soluble lysosomal protein, but without a specified lysosomal activity. A recently proposed activity from studies of the social amoeba, *Dictyostelium discoideum*, is that CLN5 may function as a glycoside hydrolase; however, this requires further validation in mammalian systems [60].

Consistent with its localization to the lysosomal lumen, CLN5 is heavily glycosylated [61, 62]. CLN5 is translated as a single transmembrane domain containing protein [59, 63], but then undergoes N-terminal cleavage in the ER by a member of the signal peptide peptidase (SPP) and SSP-like (SSPL) family, after which it is then further transported as a soluble protein [61, 64, 65]. However, the mechanism by which CLN5 is transported to the lysosome is not yet fully defined. Interestingly, neither the mannose-6-phosphate receptor (MPR)-mediated nor the sortilin-mediated pathway were essential for CLN5 transport, as lysosomal localization of CLN5 could be detected in both MPR-deficient and sortilin-deficient cell models [61, 66], indicating that the NCL protein may utilize an alternative transport route. Many of the pathogenic mutations prevent the protein from exiting the ER, underlining that a proper CLN5 localization is important for lysosomal homeostasis [61, 67]. Notably, CLN5 has been reported to interact with several other NCL proteins, among them CLN8 [68]. Therefore, one hypothesis is that CLN5 may follow the newly identified CLN8-mediated route for the transport of lysosomal proteins from the ER to ERGIC, which is discussed further in the CLN8 section of this review [54].

Conversely, in the absence of CLN5, Mamo et al. found a pronounced degradation of MPR and sortilin in the lysosome, most likely attributable to a defective recycling machinery that usually traffics the lysosomal sorting receptors from the endosomes back to the Golgi [66]. The authors showed that functional CLN5 is crucial to recruit and activate rab7, which in turn initiates the recruitment of the retromer complex to the endosomes [66]. The mechanism by which CLN5 regulates rab7 activity has not yet been delineated; however, as CLN3 has been shown to interact with both CLN5 and rab7, it might be

speculated that these proteins form a functional complex with one another [63, 69]. Besides CLN3 and CLN8, CLN5 has also been reported to interact with several other NCL proteins, such as PPT1, TPP1, and CLN6[60, 68]; it has therefore been proposed that CLN5 may be a key molecule linking different NCL-related proteins[68], perhaps accompanying their trafficking.

GRN- The role of progranulin in neurodegenerative diseases has recently been covered in detail in several reviews [70-72]. It was identified as a causal gene for autosomal recessive NCL (CLN11) in 2012, but *GRN* mutations were first connected to autosomal dominant frontotemporal lobar degeneration (FTLD) [73]. Thus, it appears that gene dosage differences give rise to two different neurodegenerative conditions, but there is also growing evidence that there are common disease mechanisms in NCL and FTLD tied to the lysosomal function of progranulin. Progranulin is initially translated in the ER and is subsequently sorted via the Golgi into secretory vesicles for regulated exocytosis. As a result, progranulin is released into the extracellular space and can be detected in biological liquids, like cerebrospinal fluid and blood [74, 75]. In the extracellular space, it may be proteolytically processed into smaller peptides (granulins), or, alternatively, it can undergo reuptake via sortilin interaction and endocytosis, which ultimately delivers progranulin to lysosomes [76]. For a fraction of progranulin, the coordinated trafficking along with another progranulin interactor, prosaposin, may also provide a direct delivery route to the lysosome [77]. A thorough understanding of the biological functions of the full-length protein and its cleavage products has not yet been achieved, but roles in regulating inflammation, wound healing, cellular proliferation, and lysosomal function are described (as reviewed in [70-72]). In a recent study, it was hypothesized that progranulin might have a role in lysosomal lipid homeostasis, since a lipidome and transcriptome analysis of human brain tissue, as well as mouse brain and liver, revealed progranulin dosage-dependent changes in the metabolism of long, polyunsaturated triacylglycerides (TAGs)[78]. Evers et al. reported that TAGs were upregulated in GRN-deficient samples, whereas phosphatidylserines and

diacylglycerides (DAGs) were reduced. A concomitant change in the expression of genes involved in lipid metabolism, lysosomal function and immune regulation was also observed [78].

Lysosomal membrane proteins in CLN3, CLN7 and CLN12 disease:

CLN3- The most common form of NCL results from mutations in *CLN3*. Despite a lot of research effort since the discovery of the *CLN3* gene, the function of CLN3 remains elusive (see [79] for a more comprehensive review on CLN3 characterization). The low expression levels and the hydrophobic nature of the protein have hampered its full biochemical characterization. It has nevertheless been shown that CLN3 is heavily glycosylated and phosphorylated and is primarily an endolysosomal membrane protein, with no clear homology to other known proteins [5, 80-82]. A combination of experimental and *in silico* analyses predicts a membrane spanning protein, most likely with 6 transmembrane domains, consistent with a possible function as a transporter or ion channel [83, 84]. Earlier studies suggested CLN3 may transport arginine or glutamate, or that it may function as a proton channel, due to observations that CLN3-deficiency models displayed an altered lysosomal pH and altered lysosomal amino acid levels, but a direct activity as an amino acid transporter or proton channel has not been shown, and it is therefore more likely that these are indirect effects of loss of CLN3 function[85-90].

Numerous studies have now linked CLN3 to a role in regulating trafficking within the endolysosomal system (reviewed in [79]). Some hypotheses as to how CLN3 may regulate trafficking include through regulation of lipid metabolism and microdomains [91-96], a regulation of vesicular movement along the cytoskeleton [69, 97], and/or via regulation of Rab7- and Cdc42-mediated vesicular trafficking and fusion, possibly playing a role in GTP/GDP cycling [69, 98, 99]. Indeed, an impact of CLN3 loss of function is a more general lysosomal dyshomeostasis [100], including a deficiency in multiple lysosomal enzymes [53, 95, 101, 102], ionic balance [103, 104], and autophagy-lysosomal pathway flux [105, 106]. This is likely to also impact lysosomal communication with other organelles, as it is now

understood that lysosomes serve as a metabolic signaling hub [107-109], also communicating with other membrane bound organelles [110, 111]. The common finding that CLN3 deficiency also leads to early-stage abnormalities in the Golgi and mitochondria supports this hypothesis (e.g. [53, 93, 112-116]). Taken together, the in-depth work surrounding CLN3 and loss-of-function phenotypes in disease models has yielded much knowledge, including identifying intriguing molecular overlap between the perturbed pathways in CLN3 disease and other neurodegenerative diseases, such as Alzheimer's and Parkinson's disease [19, 117]. However, further progress is still needed to link these observations to the primary function of CLN3, which is yet to be resolved. As a conserved protein down to unicellular organisms, its function is clearly important for cells. Work in yeast, where it was linked to the conserved Tor pathway, suggests that CLN3 is necessary for the cell's response to certain stresses [118]. Consistent with this, CLN3 function has been linked to oxidative and osmotic stress response in diverse organisms including *Dictyostelium*, fly and mouse [53, 93, 114, 119-121].

MFSD8- The gene mutated in CLN7 disease, *MFSD8*, encodes a polytopic lysosomal membrane protein (MFSD8) that shares sequence homology with the drug:H+ antiporter family DHA1 of the major facilitator superfamily (MFS) [122-124]. However, whether MFSD8 functions as a transporter and what it transports is not yet known. MFSD8 is proteolytically cleaved in the lysosome [123]. Interestingly, disease-associated mutations so far studied do not result in a mislocalization of the protein, but rather in their enhanced proteolytic cleavage, suggesting the mutations lead to a loss-of-function due to enhanced CLN7 lysosomal proteolysis [123].

Recently generated *Mfsd8*$^{-/-}$ knockout mice recapitulate the pathological and histological features of CLN7 disease, including accumulation of lysosomal storage material in brain and retina, neuroinflammation, neurodegeneration and altered autophagy [125-127]. To gain further insights into the lysosomal dysfunction in the absence of MFSD8, Danyukova et al. studied the proteome of purified lysosomes isolated from immortalized *Mfsd8*$^{-/-}$ mouse fibroblasts [128]. The abundance of several soluble

lysosomal proteins was reduced in the absence of the MFSD8 protein, while the expression of none of the identified membrane proteins was affected. Interestingly, CLN5 was among the most significantly reduced soluble lysosomal proteins, most likely due to an enhanced degradation by lysosomal proteases [128]. Loss of CLN7 function has been further implicated in alterations within the mTORC1 signaling pathway [128, 129], as well as lysosomal size, motility and lysosomal exocytosis[129]. Despite this significant recent progress, there remains much to be learned regarding the primary function of the MFSD8 protein and how its loss leads to the observed autophagy-lysosomal defects.

ATP13A2- *ATP13A2*, encoding a P-type ATPase, was first identified in 2006, when autosomal recessive mutations were discovered in patients with Kufor-Rakeb syndrome, an early-onset form of Parkinsonism (PARK9) [130]. This discovery supported an emerging role for the lysosome in Parkinson's disease pathophysiology (reviewed in [131] and more recently in [132]), which was further underscored when the same gene was implicated in 2012 in a single NCL family (CLN12 disease) [133].

ATP13A2 is predicted to be a lysosomal P5-type ATPase, which is a family of energy-driven transporters of various substrates like cations, heavy metals, and lipids [134, 135]. Because ATP13A2 was found to be implicated in zinc and manganese homeostasis, it might function as a transporter for those metals [136-140]. However, this has not yet been directly demonstrated. Intriguingly, Holemans et al. discovered that ATP13A2 is activated by lysosomal signaling lipids through a binding interaction in its N-terminus, which initiates its autophosphorylation [141]. This signaling event conferred the neuroprotective activity of ATP13A2 [141]; ATP13A2 activity is known to be protective under certain conditions of cellular stress, such as oxidative stress, metal exposure and alpha-synuclein mediated toxicity [136, 141-144]. ATP13A2 appears to promote autophagosome-lysosome fusion by facilitating recruitment of histone deacetylase 6 (HDAC6) to the lysosomal membrane [145]. A role for ATP13A2 in membrane trafficking and in the promotion of the autophagy-lysosomal pathway is consistent with the observations of altered lysosomal morphology, storage material accumulation, α-synuclein aggregation,

and impaired mitochondrial function in ATP13A2-deficiency disease models and patient cells [137, 138, 146-153].

Endoplasmic reticulum (ER) localized proteins in CLN6 and CLN8 disease:

CLN6- Despite encoding resident proteins of the ER, autosomal recessive loss-of-function mutations in *CLN6* and *CLN8* lead to a disruption in lysosomal homeostasis [12, 13, 154-157]. The ER is the site for the assembly of newly synthesized proteins, which are subsequently transported to their final location via the Golgi apparatus and secretory vesicles. The ER is also an important site for lipid biosynthesis.

CLN6 possesses seven membrane-spanning domains and appears to solely localize to the ER [12, 154, 155]. Mutated CLN6 proteins are retained in the ER and are subjected to ER associated degradation (ERAD) [157, 158], consistent with a loss of CLN6 ER function as the primary molecular defect in CLN6 disease. However, the primary biological function of CLN6 is largely unknown, and the mechanisms by which loss of CLN6 function in the ER leads to lysosomal deficiencies is still poorly understood. Nevertheless, several studies support a role for CLN6 in regulation of the autophagy-lysosome pathway. For example, in addition to displaying progressively accumulating NCL-type lysosomal storage material [159], the naturally occurring CLN6 mouse model, *Cln6^{nclf}*, also exhibits markers of autophagy impairment, including an accumulation of autophagic vacuoles, p62 aggregates, and an increase in LC3-II puncta, while ER stress or unfolded protein response (UPR) activation were not immediately evident [156]. An involvement of CLN6 in autophagic clearance is further supported by two more recent studies showing alterations in autophagy markers in primary neural cultures from naturally occurring CLN6-deficient sheep [160], and in *Cln6^{nclf}* mice, in the photoreceptor layer of the retina [161]. Interestingly, a recent paper has identified CLN6 as an interactor with the heat shock protein αB-crystallin, which suppressed the accumulation of a disease mutant version that is prone to aggregration, an effect that was abolished upon

lysosomal inhibition; the authors suggest this implies that CLN6 plays a protective role, via an autophagy-lysosome dependent process, in the cellular response to proteins that are prone to aggregation [162]. CLN6 may play a role in the initiation of autophagy, which is known to involve signaling from ER-associated complexes and ER-derived tubulovesicular membranes (e.g. [163-166]), or perhaps CLN6 supports the translation and/or transport of autophagy initiating or lysosome-targeted proteins, interacting with CLN8. Further studies are needed to test these and other hypotheses surrounding the precise role that CLN6 plays in regulating the autophagy-lysosome pathway.

A role for CLN6 in biometal homeostasis has also been suggested, from studies in both the sheep and mouse models of CLN6 disease. In both models, accumulations of zinc, copper, magnesium, manganese and cobalt were observed in distinct brain regions that were associated with *CLN6/Cln6* mutant transcript expression levels, which was proposed to possibly be connected to the Zip7 cationic transporter of the ER/Golgi [167, 168]. Later studies in primary cortical mouse neurons demonstrated that CLN6-deficiency was accompanied by a reduced expression of *Zip7*, and that pharmacological treatment with a zinc metal complex, $Zn^{II}(atsm)$, could partially correct the Zn-related abnormalities [169].

CLN8- While CLN6 localizes specifically to the ER, CLN8 cycles between the ER and the ER-Golgi intermediate compartment (ERGIC) [13, 170]. CLN8 is a ubiquitously expressed membrane-spanning protein and contains a KKXX sorting motif, in this case a Lys-Lys-Arg-Pro (KKRP) sequence, in its C-terminus, which is necessary for Golgi-to-ER retrieval and for binding to coat-protein I (COPI) [13, 171]. di Ronza et al. have recently reported that CLN8 deficiency causes the depletion of a number of soluble proteins in the lysosome, and it was demonstrated that CLN8 is a receptor binding to and aiding in the transport of a subset of soluble lysosomal proteins out of the ER for further processing in the Golgi; the subset of enzymes requiring CLN8 for their transport and maturation included the NCL-related enzymes CTSD, CTSF, TPP1, PPT1, as well as some other soluble lysosomal proteins [54]. The second luminal loop was characterized as a site for cargo binding, and the KKXX motif was crucial for the maturation of lysosomal

enzymes [54]. In line with this, disease mutations mapped to the second luminal loop weakened CLN8 interaction with lysosomal cargo, suggesting that the ability of CLN8 to bind lysosomal cargo and traffic between the ER and Golgi compartments is crucial for lysosomal biogenesis [54].

CLN8 also belongs to the family of TRAM-Lag1p-CLN8 (TLC)-domain containing proteins, based on multiple sequence alignment which has led to the hypothesis that CLN8 functions in lipid synthesis, transport or sensing [172]. Although experimental data supporting a mechanistic link between CLN8 and lipid biosynthesis/homeostasis are lacking, several studies in mouse models and patient tissue suggest a dysregulation in lipid metabolism upon loss of CLN8 function (e.g. [173-175]). One possible alternative explanation for these observations may be that CLN8 indirectly regulates lipid metabolism through its role in directing the transport and maturation of lysosomal proteins important for lipid catabolism, given the recent research by di Ronza et al., described above [54].

Non-lysosomal proteins in CLN4 and CLN14 disease:

DNAJC5- *DNAJC5,* identified as the causal gene in adult-onset CLN4 disease, encodes cysteine-string protein alpha (CSPα), which is an abundant chaperone protein in neurons that is found in close proximity to synaptic terminal membranes, rather than to the endo-lysosomal compartment [14, 176-180]. As a chaperone, it has an important role in protein folding and stability of various synaptic proteins. In particular, it facilitates the assembly of the SNARE complex, which is required for fusion and exocytosis of synaptic vesicles [181], and CSPα levels have been linked to synaptic degeneration [182]. A number of additional, so-called "client" proteins have been assigned as CSPα substrates, including presynaptic ion channels, signaling proteins and proteins implicated in synaptic vesicle release [183]. Importantly, CSPα is one of the most highly palmitoylated proteins in the brain, undergoing palmitoylation in the highly conserved cysteine-string domain; in CLN4 patients, the disease mutations identified to date all converge on this domain, and have been shown to impact subcellular localization and membrane association [176,

184]. However, it is not yet understood how the mutations seen in CLN4 patients impact the lysosome and lead to the profound lysosomal ceroid lipofuscin accumulation that is observed in patient brain. Some initial clues have emerged in the recent literature. In a recent study by Nieto-González et al., CSPα function has been linked to the mTOR signaling pathway. In this study, the authors found a hyperactivation of the mTOR pathway causing hyperproliferation of neurospheres generated from CSPα-deficient mice, although the precise mechanism by which this occurs is not yet resolved [185]. mTOR signaling is highly connected to lysosomal metabolism being influenced by lysosomal signals and negatively regulating autophagy [107, 109]. In a second recent study, an intriguing potential association between CSPα and the lysosome was made. Wyant et al. recently reported a quantitative proteome of lysosomal proteins under different nutrient levels, where CSPα (denoted as DNAJC5 in the study), but not α-synuclein, was among the hits and CSPα was even more abundant in the lysosome under starvation conditions (see DNAJC5 in Supplementary Table 2, [186]). Thus, CSPα may also have a direct role in the lysosome, perhaps in chaperoning lysosomal protein complexes. Further studies are needed to fully elucidate a putative lysosomal function for CSPα.

KCTD7- *KCTD7* mutations were found in a family with a variant form of infantile-onset NCL, giving it the designation of CLN14 [187]. KCTD7 is member of the potassium channel tetramerization domain-containing protein family. Members of this family possess an N-terminal Bric-a-brack, Tram-track, Broad complex (BTB), or POZ domain, a protein-protein interaction motif that is also homologous to the T1 tetramerization domain of voltage-gated potassium channels [188]. Importantly, however, there is no evidence that KCTD protein family members themselves are potassium channels, but rather they play a role in the ubiquitin pathway, through cullin-3 (CUL3) interaction, likely linking target proteins to the E3 ubiquitin ligase complex [188]. KCTD7 interaction with CUL3 was abolished by the identified KCTD7 mutations in CLN14 patients [187].

KCTD7 is thought to primarily localize to the cytoplasm and to the plasma membrane. It has been suggested that KCTD7 may regulate potassium conductance [189]. More recently, Moen et al. reported that, in Xenopus oocytes, KCTD7 caused a K+-dependent hyperpolarization of cells, which modulated activity of Slc38a2, the neuronal glutamine transporter, and that KCTD7-disease associated mutations did not display this same activity [190]. Therefore, KCTD7 may modulate neural signaling and transmission and loss of this function may lead to progressive myoclonic epilepsy [189, 190].

Intriguingly, recent studies also suggest a role for KCTD7 in the regulation of autophagy-lysosomal pathways. In patient brain and fibroblasts and in yeast deleted for *WHI2*, which encodes a protein that has sequence similarity to KCTD family members, autophagosomal and lysosomal morphological abnormalities were observed, and reduced initiation of autophagy and autophagic flux was demonstrated under low nutrient conditions [191]. Metz et al. also observed accumulating mitochondrial abnormalities in KCTD7 patient fibroblasts, consistent with a defect in autophagy and/or mitophagy [191]. These effects on autophagy upon loss of KCTD7 may be mediated through its CUL3 interaction, as CUL3 has been linked to the regulation of several key autophagy regulatory proteins through its association with KLHL20, an E3 ubiquitin ligase, including ULK1 which is required for autophagy initiation [192]. CUL3 has also been linked to the regulation of late steps in the endolysosomal pathway, as CUL3 knockdown caused a defect in late endosome-lysosome maturation and disrupted the efficient lysosomal degradation of the EGF receptor in HeLa and A549 cells [193]. Despite this emerging evidence about the importance of KCTD7 on autophagy-lysosomal function, it is noteworthy that the majority of patients with *KCTD7* mutations are reported to lack NCL-type storage material, although abnormal lysosomal features and lipofuscin are more commonly observed [191, 194]. These pathology discrepancies may be due to the difficulties associated with the classification of storage material [195], or other genomic or environmental factors may modify this disease feature. Therefore, future research will be required to shed further light on the role of KCTD7 in

autophagy-lysosomal function and on the occurrence of lysosomal storage material in KCTD7-related disease.

GENOTYPE-PHENOTYPE CORRELATIONS IN THE NCLS AND RELATED DISORDERS

With the clinical application of new sequencing technologies in genetic disease diagnosis, it is increasingly recognized that NCL genes with 'milder' mutations (commonly missense mutations) can lead to milder disease, or even what is clinically described as a different disease [6, 196, 197]. Table 2 summarizes the NCL genes associated with alternative disease diagnoses. A rare recessive form of ataxia, spinocerebellar ataxia, recessive type 7 (SCAR7) is due to mutations in *TPP1*[198], which classically causes late infantile CLN2 disease [11]. Non-syndromic retinal degeneration and non-syndromic autophagic vacuolar myopathy have each been linked to mutations in *CLN3*, which classically causes juvenile NCL [5], or juvenile CLN3 disease. Similarly, mutations in *CLN7* have been identified in cases of nonsyndromic eye disease [199]. *CLN6*, first identified in 2005 as the causal gene in a variant form of late infantile NCL [154, 155], was surprisingly later also linked to adult-onset NCL, alternatively named Kufs disease, type A, which lacks visual impairment as a disease feature [200]. *CLN8* is identified as an NCL gene (CLN8 disease), but was first identified as the causal gene in the phenotype known as Northern epilepsy or progressive epilepsy with mental retardation [201]. Mutations in *KCTD7* are well recognized to cause progressive myoclonic epilepsy (PME) [191, 202], but in some rarer cases have also been associated with PME accompanied by vision loss and lysosomal storage and termed an NCL [187, 194]. *ATP13A2* was identified as causing NCL in dogs [203], with mutations in *ATP13A2* first described in a rare form of Parkinsonism called Kufor-Rakeb syndrome [130] and, later, in one family with fingerprint-type storage material diagnosed with NCL [204]. Accumulation of NCL-type storage material and α-synuclein, and late-onset impairment in sensorimotor functioning, was reported in *Atp13a2* knockout mice, which suggests ATP13A2-related disease may represent a unique disorder with features overlapping with both NCL and Parkinson's disease [150]. More recently, mutations in *ATP13A2* have been reported in multiple families

with a later-onset autosomal recessive spastic paraplegia 78 (SPG78) [205, 206]. Notably, lysosomal pathology was reported in fibroblasts from some of these SPG78 patients, suggesting this clinical phenotype may also have significant pathophysiologic overlap with the other forms of ATP13A2-associated disease [206]. Finally, *GRN*, encoding progranulin, was identified as a rare cause of NCL with onset in early adulthood when bi-allelic mutations were present, while the same mutations lead to frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) when present on one chromosome only [73]. Autosomal dominant *GRN* mutations in FTLD patients cause disease through haploinsufficiency [207] in contrast to all other recessive NCLs where mutation carriers are healthy. Intriguingly, similar to the case for *ATP13A2*, there is increasing evidence that both NCL-related and FTLD-related features are observed in the context of both autosomal dominant and autosomal recessive *GRN* mutations, again suggesting commonalities in the underlying disease pathogenic mechanisms. Ward et al. were the first to report NCL-type pathology in FTLD patients with progranulin haploinsufficiency, demonstrating autofluorescent, NCL-like storage material in FTLD patient retina, postmortem brain and lymphoblasts [208]. Similarly, Valdez et al. observed both TDP-43 inclusions and lipofuscin with NCL-like features in neurons derived from FTLD patient induced pluripotent stem cells [52]. *Grn* knockout mice also exhibit both NCL-like and FTLD-like features, including progressive accumulation of NCL-type storage material, neuroinflammation, late onset of behavioral deficits, and an accumulation of ubiquitin and TDP-43 inclusions [209-211].

Thus, in many cases where NCL genes are associated with protracted or alternative disorders, either the gene dosage or the specific mutations appear to correlate with clinical phenotype. A significant amount of this variation in clinical phenotype may be explained by differing levels of residual protein function. However, it is also likely that co-inheritance of other genetic variations could influence these varying phenotypic pictures. Nevertheless, this progress provides compelling evidence that the underlying

pathogenic mechanisms are likely to be at least partly shared between classical forms of NCL and the alternative disease forms.

OUTLOOK

As for many inherited diseases, the NCLs are entering a new era of genomics, in which defining gene interactions, epigenetics, and gene-environment interactions will be critical to understand the increasingly complex NCL genotype-phenotype relationships and to make progress in developing, refining and monitoring the efficacy of treatments for this heterogeneous group of rare disorders. Given the increasing evidence that the NCLs share causal genes and/or molecular and pathologic overlaps with more prevalent disorders, such as Alzheimer's and Parkinson's disease and FTLD, it is likely that knowledge gained in the NCLs will also lead to key insights into the molecular pathogenesis of those disorders as well.

Future progress in NCL genomics will require greater cross-discipline collaboration and increased curation of robust clinical phenotype data, matched to genomic information and biological samples from NCL patients. To this end, continued documentation of validated genomic variation associated with the NCLs in publicly available databases, such as the NCL Mutation Database (https://www.ucl.ac.uk/ncl-disease/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), is critical to the future success of disease diagnosis and treatment. This greater understanding of NCL genomics and the current focus on development of new therapies will support the requirement for and possibility of more rapid and earlier diagnosis to reach the best clinical outcome for any affected by NCL. This will require changes in national policies.

We are moving towards a future era of genomic medicine, where full genomic information is required to design the best clinical care for an individual. In the future, we can anticipate that personalized treatment approaches, tailored to the underlying mutation and the genetic background of each patient, will be possible for the neuronal ceroid lipofuscinoses.

FUNDING

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Table 1. A summary of the genetically distinct forms of CLN disease (NCL)

Disease					Gene	Protein			
Disease	Typical clinical Phenotype (age of onset)	Early Symptoms and Signs	EM inclusion profile/ Storage material, if known	OMIM	Gene	Protein	Primary Localization	Predicted function	Pathways implicated
CLN1	Classic infantile (6-24 mos)	Loss of developmental gains, seizures, myoclonus, later visual failure	GROD/ saposins	256730	*PPT1*	Palmitoyl protein thioesterase 1 (PPT1)	Lysosomal lumen, synaptic vesicles	Cleavage of S-Palmitoylation	Lysosomal protein degradation neurotransmission, homeostatic synaptic plasticity
CLN2	Classic late-infantile (2-4 yrs)	Difficult to control seizures, speech or motor difficulties, myoclonus, developmental and visual failure	CL/ subunit c	204500	*TPP1**	Tripeptidyl peptidase 1 (TPP1)	Lysosomal lumen	Serine protease	Lysosomal protein degradation
CLN3	Classic juvenile (4-10 yrs)	Visual failure, dementia, behavioral and motor difficulties, later onset of seizures	FP/ subunit c	204200	*CLN3**	CLN3	Endolysosomal membrane	Unknown	Autophagy; lipid metabolism; endo-lysosomal trafficking, lysosomal homeostasis, TOR signaling
CLN4	Adult, Kufs disease (Parry type) (teens to 30+ yrs)	Seizures, ataxia, myoclonus, behavioural changes, dementia (no visual failure)	GROD/ saposins	162350	*DNAJC5*	Cysteine-string protein alpha (CSPα)	Cytosol, association with lysosome	Chaperone	Synaptic vesicle recycling, folding and stabilization of lysosomal proteins
CLN5 (CLN9)	Variant late infantile (3-7 yrs)	Abnormal behavior, cognitive decline, seizures, visual failure, myoclonus, motor difficulties	CL, FP, RL/ subunit c	256731	*CLN5*	CLN5	Lysosomal lumen	Unknown	Endolysosomal vesicle trafficking; lipid metabolism
CLN6	Variant late infantile (1.5-8 yrs), also adult (Kufs type A disease; 16-51 yrs)	Late infantile= seizures, myoclonus, motor difficulties, visual failure, cognitive decline, adult=progressive myoclonic epilepsy	FP, CL, GROD/ subunit c and saposins	601780	*CLN6*	CLN6	ER membrane	Unknown	Autophagy; metal homeostasis
CLN7	Variant late infantile (1.5-8 yrs)	Seizures, myoclonus, developmental regression, visual failure, cognitive decline	RL, FP/ subunit c	610951	*MFSD8*	MFSD8	Endolysosomal membrane	Putative transporter	Sorting and trafficking of lysosomal enzymes; autophagy; mTOR signaling
CLN8	Variant late infantile (1.5-7 yrs)	Myoclonic seizures, visual failure, ataxia, cognitive decline	GROD, CL, FP/saposins and subunit c	600143	*CLN8**	CLN8	ER/ ERGIC membrane	Trafficking receptor	Maturation and sorting of lysosomal enzymes; lipid synthesis and transport

CLN10	Congenital (neonatal)	Epileptic encephalopathy, microcephaly	GROD/saposins	610127	*CTSD*	Cathepsin D	Lysosomal lumen	Aspartic protease	Lysosomal protein degradation
CLN11	Adult (early 20s)	Visual failure, myoclonic seizures, ataxia, dementia	GROD, FP/subunit c and saposins	614706	*GRN**	Progranulin	Lysosomal lumen	Unknown	Inflammation; lipid regulation; lysosomal function
CLN12	Juvenile, pre-teen (8-12 yrs)	Ataxia, dementia, parkinsonism	FP/subunit c	606693	*ATP13A2**	ATP13A2, Park9	Endolysosomal membrane	Transporter	Metal homeostasis; oxidative stress; autophagosome-lysosome fusion
CLN13	Adult (Kufs type B disease; 20+ yrs)	Ataxia, tremor, dementia, rare seizures	FP (brain)	615362	*CTSF*	Cathepsin F	Lysosomal lumen	Cysteine protease	Lysosomal protein degradation
CLN14	Infantile (8-9 mos)	Myoclonus epilepsy, motor and speech regression, visual failure	FP, GROD	611726	*KCTD7**	Potassium channel tetramerization domain-containing protein 7 (KCTD7)	Plasma membrane, cytosol	CUL3-E3 ubiquitin ligase linker	K^+ conductance; autophagosome-lysosome function

*Indicates genes identified in other clinical phenotypes/diseases (see further details in Table 2)

Abbreviations= GROD, granular osmiophilic deposits; CL, curvilinear; FP, fingerprint; RL, rectilinear

Table 2. Other clinical phenotypes/diseases associated with NCL genes

Gene	NCL syndrome	Alternative phenotype/disease
TPP1	CLN2 disease, late infantile	Spincocerebellar ataxia, recessive type 7 (SCAR7)
CLN3	CLN3 disease, juvenile	Autophagic vacuolar myopathy
CLN3	CLN3 disease, juvenile	Non-syndromic retinal degeneration (retinitis pigmentosa, adult cone-rod dystrophy)
CLN6	CLN6 disease, late infantile	Adult onset Kufs type A, without vision loss
CLN6	CLN6 disease, late infantile	Juvenile cerebellar ataxia
CLN7	CLN7 disease, late infantile	Non-syndromic retinal degeneration (adult macular dystrophy adult cone-rod dystrophy)
CLN8	CLN8 disease, late infantile	Northern epilepsy, without vision loss, also known as Progressive Epilepsy with Mental Retardation
GRN	CLN11 disease, adult	Frontotemporal lobar degeneration with TDP-43 inclusions
ATP13A2	CLN12 disease, juvenile	Kufor-Rakeb syndrome (with Parkinsonism)
ATP13A2	CLN12 disease, juvenile	Spastic paraplegia 78, autosomal recessive
ATP13A2	CLN12 disease, juvenile	Juvenile onset amyotrophic lateral sclerosis
KCTD7	CLN14 disease, infantile	Progressive myoclonic epilepsy-3, without NCL-type lysosomal storage
KCTD7	CLN14 disease, infantile	Opsoclonus-myoclonus ataxia-like syndrome