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Neuronal Ceroid Lipofuscinosis: Impact of Recent Genetic Advances and Expansion of the Clinicopathologic Spectrum

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Abstract

Neuronal ceroid lipofuscinosis (NCL), first clinically described in 1826 and pathologically defined in the 1960s, refers to a group of disorders mostly diagnosed in the childhood years that involve the accumulation of lysosomal storage material with characteristic ultrastructure and prominent neurodegenerative features including vision loss, seizures, motor and cognitive function deterioration, and oftentimes, psychiatric disturbances. All NCL disorders evidence early morbidity, and treatment options are limited to symptomatic and palliative care. While distinct genetic forms of NCL have long been recognized, recent genetic advances are considerably widening the NCL genotypic and phenotypic spectrum, highlighting significant overlap with other neurodegenerative diseases. This review will discuss these recent advances and the expanded potential for increased awareness and new research that will ultimately lead to effective treatments for NCL and related disorders.

Keywords

neuronal ceroid lipofuscinosis; NCL; Batten disease; Kufs disease; Parkinson's disease; parkinsonism; frontotemporal lobar degeneration; FTL; endosome; lysosome; lysosomal disease; subunit c; saposin; progranulin; DNAJC5; CSP ; CLN6; cathepsin F; KCTD7; ATP13A2

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Introduction

The NCL disorders, sometimes referred to as Batten disease, are pan-ethnic neurodegenerative disorders that affect all age groups and are mostly inherited in an autosomal recessive fashion, although autosomal dominant forms are also recognized (for a detailed reference see [1]). While currently reliable worldwide incidence estimates are not available, country-specific estimates typically range from 1 to 2.5 in 100,000 live births, with enrichment in some geographic regions, such as within the Scandinavian Peninsula (Appendix 1 in [1]).

Infantile and childhood forms of NCL are the most common and are characterized by visual failure that progresses to blindness, behavioral problems, onset of seizures, loss of cognitive and motor function (developmental regression) and ultimately, premature death. The less common early-adult forms tend to present with early dementia, myoclonic seizures, movement abnormalities (ataxia, extrapyramidal), and sometimes, psychiatric disturbance, and lack visual involvement [1]. Onset and progression of the clinical manifestations of NCL can be very heterogeneous, even within families [2-4]. A hallmark of NCL is the histopathologic finding of lysosomal autofluorescent lipopigments in brain and other tissue types, which display a distinctive ultrastructural pattern by electron microscopy (EM) described as curvilinear (CV), rectilinear (RL), fingerprint (FP) or granular osmiophilic deposit (GROD) profiles, and predominantly contain the lipophilic proteins subunit c of the mitochondrial ATP synthase and/or the sphingolipid activator proteins, saposins A and D (SAPs) (Table 1) [1, 5].

Solving the molecular basis of the NCL disorders began in 1995 with the discovery in the same year of palmitoyl protein thioesterase 1 (PPT1), a soluble lysosomal enzyme encoded by the *PPT1* gene (sometimes referred to as *CLN1*) [6], and the *CLN3* gene, encoding a putative lysosomal membrane protein [7]. In the following years, mutations in 6 more genes were shown to cause NCL: *TPP1* (sometimes referred to as *CLN2*) in 1997 [8], *CLN5* in 1998 [9], *CLN8* in 1999 [10], *CLN6* in 2002 [11, 12], *CLN10/CTSD*, encoding cathepsin D, in 2006 [13] and *CLN7/MSFD8* in 2007 [14] (Table 1). Nearly two decades of research have uncovered important roles for the NCL proteins in lysosomal catabolism and recycling of proteins and lipids, though the precise functions of most NCL proteins remain unsolved. Kousi and colleagues have recently reviewed the spectrum of mutations in these NCL genes [15], and Kollmann and colleagues have recently reviewed the current understanding of the NCL proteins [16]. Of note is the discovery that distinct sets of *CLN6* mutations cause two forms of NCL. A severe form, thought to result from complete loss of function mutations, displays lysosomal storage primarily of the FP and RL types, and clinical symptom onset in the late infantile years presenting with seizures, followed by severe vision loss, ataxia, mental regression and death in the mid twenties [11, 12]. A milder, early-adult onset form, thought to result from mutations that cause reduced protein activity but not a complete loss of function, displays lysosomal storage primarily of the FP and GROD types, presents with progressive myoclonic epilepsy (PME) alone, and does not involve visual failure [17].

Here we will review the most recent discoveries in NCL genetics, which underscore the need for further studies aimed at elaborating the functions of the NCL proteins and genotype-phenotype relationships. Once attained, these insights will have great potential to impact our understanding, recognition and treatment of NCL and related disorders.

Recent genetic advances broaden understanding of the molecular basis of the NCL disorders

While more than a decade of genetic research into the molecular causes of recessive, infantile and childhood-onset NCL yielded the eight key NCL genes mentioned above, most cases of adult-onset NCL (sometimes referred to as Kufs disease), and some infantile/childhood-onset cases, have remained unsolved until recently. Technological advances and dropping costs of next generation sequencing have led to the discovery of five additional NCL genes in the past year (Table 1).

CLN4

Multiple groups identified a major cause of autosomal dominant adult-onset NCL, using a combination of classic linkage approaches and whole exome sequencing (WES). Noskova and colleagues initially reported the identification of two different mutations in *DNAJC5* in independent families with NCL-like clinical features and GROD-type storage material [18]. The same mutations were confirmed in three subsequent WES reports [19-21]. *DNAJC5* encodes cysteine-string protein alpha (CSP), a chaperone protein highly expressed in brain and known to be heavily palmitoylated in a manner that influences synaptic vesicle membrane association (reviewed in [22]). Though its precise function is not fully understood, CSP appears to serve an important role in neuronal synaptic activity through regulation of SNARE protein levels, and CSP is required for activity dependent neuronal cell survival [23, 24]. The NCL-associated CSP mutations, p.Leu116del and p.Leu115Arg, which have arisen independently multiple times [18, 21], impact the palmitoylated cysteine-string domain. Evidence suggests these mutations likely lead to higher order CSP self-aggregation, possibly also incorporating wildtype CSP protein into the aggregates, causing a toxic gain-of-function [25]. In light of this discovery, it is intriguing that PPT1 catabolizes the palmitoyl linkages on protein substrates [26] and that CLN3 has been proposed to be involved in regulating saturation of palmitoylated side chains, which may regulate protein trafficking [27, 28]. Like CSP, both PPT1 and CLN3 have been localized at or near the synapse, in vesicles and in the plasma membrane [29-32]. Specific PPT1 and CLN3 palmitoylated substrates have not yet been identified, though several (including CSP) have been proposed [33, 28]. Whether palmitoylated CSP is a substrate for PPT1 or CLN3-mediated activities requires further experimental testing.

CLN11

Smith and colleagues recently reported on a pair of siblings with a recessive form of NCL, with vision loss and seizure onset in their late 20s and skin biopsy evidence of NCL-like storage material of the FP type [34]. WES identified a homozygous progranulin (*GRN*) mutation that was identical to that previously seen with an autosomal dominant inheritance pattern in frontotemporal lobar degeneration with ubiquitinated TDP-43 inclusions (FTLD-TDP) [34]. Progranulin, most recently reviewed by Cenik et al [35] and Jian et al [36], is a secreted protein that is localized within the endoplasmic reticulum (ER) and endosomal-lysosomal system and undergoes proteolytic processing into the low molecular weight granulins. The functions of progranulin and the cleaved granulins are unknown, but their expression is particularly high in neurons and activated immune cells [37-39], suggesting they are likely to play an important role in neuronal function and inflammation [35, 36]. Intriguingly, progranulin has also been demonstrated to bind sortilin, which is thought to direct its trafficking into the endosomal-lysosomal system [40]. It is noteworthy that interactions between other NCL-related proteins and sortilin and/or its retrograde trafficking receptor, retromer, have also been demonstrated [41-43, 28], highlighting further commonalities among at least several forms of NCL (Figure 1). The potential overlap in

disease pathophysiology between *GRN*-associated NCL and FTLD raised by these new genetic data will be further discussed in the next section of this review.

CLN12

In 2011, a canine form of NCL was described by Wohlke and colleagues, which was due to a one base pair deletion in *ATP13A2* [44]. Subsequent to that report in 2012, Bras and colleagues reported their finding in another WES study that a homozygous missense mutation (c.T2429G/p.Met810Arg) in the same gene segregated with the disease in an NCL family with FP-type storage material [45]. *ATP13A2*, also called *PARK9*, was previously associated with Kufor-Rakeb syndrome, a rare monogenic parkinsonism disorder [46, 47]. Like a number of the other NCL genes (Table 1), *ATP13A2* encodes a transmembrane protein and is suspected of being a P-type transporter, possibly of cations or glycolipids [45, 46, 48], and overexpression studies localized the protein to the lysosomal membrane [46, 49]. The potential overlap in disease pathophysiology between *ATP13A2*-associated NCL and monogenic parkinsonism raised by this recent discovery will be further discussed in the next section of this review.

CLN13

It was previously known that mutations in the cathepsin D (*CTSD*) gene, which encodes an aspartyl protease within the endosomal-lysosomal system, lead to the most severe form of NCL, congenital NCL, and less frequently to a form of early childhood NCL [13, 50]. Perhaps not surprisingly then, a second member of the cathepsin family of proteases was also recently demonstrated to be linked to NCL. As reported by Smith and colleagues, WES of samples from a family with a recessive NCL disorder with FP-type storage material led to the identification of a homozygous missense *CTSF* mutation, encoding cathepsin F, a lysosomal cysteine protease whose *in vivo* substrates and intracellular pathway are unknown [51]. Further sequencing of the *CTSF* gene in additional NCL patient samples for which no other known gene defect was present, identified a second NCL family with compound heterozygous *CTSF* mutations. Further investigation of a *Ctsf* knock-out mouse model strongly supported these findings, as these mice likewise displayed classical NCL-like storage material and phenotypes [51].

CLN14

WES of a sib-pair with infantile-onset NCL and a mixture of FP and GROD-type lysosomal storage, uncovered a homozygous mutation in *KCTD7*, encoding potassium channel tetramerization domain containing protein 7 (*KCTD7*) [52]. Different mutations in the *KCTD7* gene have also been identified in PME patients, but without lysosomal storage [53, 54]. Given the limited number of patients with *KCTD7* mutations and for which skin biopsy lysosomal storage analysis has been performed, it remains unclear whether these observations represent a variant genotype-phenotype relationship or whether *KCTD7* mutations are more broadly associated with this key NCL feature. *KCTD7* is not yet well studied, but suspected functions include regulation of ion channels and function in the ubiquitin-proteasomal system [55]. *KCTD7* is known to interact with cullin-3 (*CUL3*), an E3 ubiquitin ligase [55]. The missense mutation reported in this NCL family disrupted the *KCTD7*-*CUL3* interaction as shown by co-immunoprecipitation studies using an overexpression system, supporting the hypothesis that the disease pathobiology involves regulation of *CUL3* function [52]. *CUL3* has also been recently recognized as playing an important role in late endosomal maturation [56], and it is known that ubiquitin modification is an important mechanism regulating protein trafficking and signaling pathways within the endosomal system [57]. Future research studies into the possible role of ubiquitin-mediated processes in NCL disease pathogenesis are warranted.

The primary neurological symptoms in the NCL disorders, and the enrichment of NCL proteins at or near the neuronal synapse, support the importance of the NCL proteins in neuronal function. A hypothetical model of NCL protein and clinical syndrome overlap is depicted in Figure 1. The NCL proteins may function in a single common pathway, or in intersecting or parallel pathways, leading to highly similar end-stage features involving lysosomal storage and neurological dysfunction. NCL gene expression data and studies in genetic models [16] also predict significant consequences of NCL gene mutations in other cell types that, like neurons, heavily rely on coordinated trafficking to and from the cell surface and that have high energy demands, including immune cells, secretory cells, and cardiomyocytes. Further targeted studies are important to understand the full impact of the NCL gene mutations and protein disruption on non-neuronal cells and organ function. Indeed, cardiac pathology in later stages of late-infantile and juvenile NCL (*CLN2* and *CLN3*, respectively), and an abnormal autoimmune response in juvenile NCL (*CLN3*) have been documented [58-60]. As a result of the latter findings, suppression of the immune system using mycophenolate mofetil (CellCept®) in *CLN3* patients is currently being tested in a Phase II clinical trial (www.clinicaltrials.gov).

Overlap between NCL and other neurological diseases

Increased understanding of the molecular basis of the NCL disorders has established compelling evidence that altered NCL gene function may be implicated in other neurological diseases (Figure 1). These discoveries augment a growing body of evidence that endosomal-lysosomal system dysfunction plays a significant role in neurodegeneration.

FTLD

After Alzheimer's disease, FTLD is the second most common form of presenile dementia, with a usual age of onset between 45 and 65 years. FTLD is broadly characterized by neurodegeneration of the frontal and temporal cortices leading to behavioral and language disturbances with usual sparing of memory and visuospatial functions. This disorder is further categorized pathologically into sub-types based on differing histologic features (see recent review [61]). FTLD-TDP is distinguished by intraneuronal cytoplasmic deposits, which are tau-negative and positive for ubiquitin and TDP-43 (an RNA-binding protein and splicing regulator encoded by *TARDBP*). The surprising finding that identical mutations in *GRN* underlie NCL and FTLD-TDP in autosomal recessive and autosomal dominant fashion, respectively, raises intriguing new questions regarding whether there are also overlapping pathophysiologies underlying these two forms of neurodegeneration [34, 35]. Notably, in addition to the core features of FTLD, FTLD-TDP associated with *GRN* mutations may also affect the basal ganglia and parietal cortex, resulting in parkinsonism, corticobasal syndrome, and memory impairment [62].

The majority of FTLD-associated *GRN* mutations lead to reduced progranulin levels and are suspected to cause disease by haploinsufficiency, rather than toxic gain-of-function mechanisms [35, 63]. Two independent *Grn*-deficient mouse lines show recessively inherited intraneuronal ubiquitin-positive, autofluorescent storage consistent with lipofuscin [38, 64], and one of these analyzed ultrastructurally displayed the characteristic appearance of NCL storage material [38, 34]. Other studies describe some behavioral abnormalities in homozygous mice, including social interaction deficits and enhanced aggression, that may be seen in clinical FTLD [65-67], but interestingly, heterozygous mice, which might be expected to model human FTLD-TDP given the suspected haploinsufficiency mechanism, have been reported to lack overt behavioral or histopathologic abnormalities [65-67]. Further studies are certain to shed more light on the intriguing relationship between progranulin and neurodegeneration.

Parkinsonism

The potential for shared disease pathophysiology between NCL and parkinsonism is also particularly intriguing. Clinical features of classical Parkinson's disease (PD) as well as monogenic forms of parkinsonism, including bradykinesia, rigidity, and to a lesser extent, resting tremor, are well-documented in later stages of juvenile NCL caused by mutations in *CLN3* [3]. Functional evidence for nigrostriatal pathology in these patients includes decreased striatal uptake of [^{18}F]-fluorodopa [68] and decreased striatal dopamine transporter density revealed by SPECT imaging using the labeled cocaine analog [^{131}I] - CIT [69]. In addition, the extrapyramidal features of juvenile NCL respond to antiparkinsonian therapy, albeit variably [70]. Parkinsonian features have also been reported in a late-infantile NCL patient with *TPP1* mutations who responded to Levodopa [71], and in a large Dutch family with NCL caused by *DNAJC5* mutation [72, 18]. Neuropathology of an unrelated *DNAJC5* patient showed considerable degeneration of the substantia nigra, consistent with parkinsonian features late in the clinical course [73, 18].

The discovery of mutations in *ATP13A2* in NCL patients provides the first genetic link between parkinsonism and NCL. While *ATP13A2/PARK9* mutations had previously been linked to Kufoor-Rakeb syndrome, without neuropathology available for these patients, it is difficult to know whether these in fact represent the same or distinct diseases. Of note, however, mice homozygous for an *Atp13a2* knock-out allele showed pathologic features of both NCL (lipofuscin deposition in the cerebellum, cortex, and hippocampus) and PD (increased insoluble α -synuclein, however, without apparent dopaminergic neuron loss or decreased striatal dopamine) [74]. Moreover, *ATP13A2* has been shown to significantly influence α -synuclein and manganese toxicity in yeast and mammalian PD models, potentially linking environmental and genetic factors influencing parkinsonism [75].

The relationship between PD and lysosomal dysfunction was previously recognized by the finding that Gaucher disease gene mutations (*GBA1*, encoding glucocerebrosidase) are also risk variants for PD (reviewed in [76]). Polymorphisms in linkage disequilibrium with the *CLN8* locus, and associated with altered *CLN8* gene expression in cultured fibroblasts, were recently implicated as possible Gaucher disease genetic modifiers [77], further supporting a hypothesis of common or intersecting biological pathways.

PME

NCL is part of the differential diagnosis of isolated PMEs, which are clinically and genetically heterogeneous epilepsy syndromes of childhood to early adulthood. The PME disorders typically have in common myoclonus (often prominent in the face and distal extremities and inducible with photic stimulation), multiple seizure types, psychomotor regression, and cerebellar signs [78]. As discussed previously, mutations in *CLN6* cause a subset of adult-onset NCL in which PME is frequently a presenting feature and visual failure does not develop [17]. Moreover, *CLN6* mutations are documented in PME patients with no evidence of lysosomal storage [79]. Similarly, patients with mutations in *KCTD7* commonly present with PME, which may or may not involve lysosomal storage. Further genotype-phenotype studies are therefore needed to better understand the relationship between lysosomal dysfunction and the *KCTD7* and *CLN6* genes.

SCAR7

A recent study has also uncovered a surprisingly expanded phenotypic spectrum for mutations in *TPP1*, the gene typically mutated in classic late-infantile NCL (*CLN2*) [80]. Affected individuals in a previously described Dutch family [81] as well as an unrelated sporadic SCAR7 case were found to be compound heterozygous for the common *TPP1* splice site mutation c.509-1G>C and the missense mutation p.Val466Gly [80]. Affected

individuals presented in childhood or adolescence with cerebellar ataxia and pyramidal signs but at the time of the report had not yet manifested seizures or ophthalmologic abnormalities. Skin biopsies were performed on 2 patients; one showed GROD and FP profiles, but not the CV profiles characteristic of classic late-infantile NCL (Table 1); the other biopsy did not show storage material. A TPP1 enzyme activity assay showed 10-15% of normal levels in peripheral blood and 5% of normal levels in cultured fibroblasts (compared to 9% and 0.4%, respectively, in the reference set of classic late-infantile NCL cases). These findings suggest that higher residual TPP1 activity produces a more protracted atypical NCL clinical course [80].

Mitochondrial disorders (primary or secondary)

The core clinical features of NCL, including pigmentary retinopathy, seizures, movement abnormalities, and regression, are also observed in a broad range of mitochondrial disorders. In some cases the major distinguishing feature identified was the diagnostic inclusions of NCL [82]. It is therefore not altogether surprising that certain subtypes of NCL show alterations in mitochondrial morphology, subcellular distribution, respiratory chain complex activity, or basal ATP synthesis [83-86]. The role of impaired mitochondrial homeostasis has been recognized in other neurodegenerative diseases, most notably PD. Mutations in DNA polymerase gamma 1 (*POLG1*), which encodes the catalytic subunit of the mitochondrial DNA polymerase, have been linked to early-onset forms of parkinsonism [87, 88]. Turnover of damaged mitochondria by a regulated form of autophagy, known as mitophagy, is impaired by mutations in *PARK2*, which encodes the ubiquitin ligase parkin [89]. Kufor-Rakeb associated mutations in *ATP13A2* have also been linked to defective mitochondrial quality control mediated by mitophagy [90], suggesting that forms of NCL caused by *ATP13A2* mutations may reveal similar pathology. Further highlighting the potential intersection between NCL and mitochondrial disease is a case report suggesting that a variant in *POLG1* (c.1550G>T, p.Gly517Val) may modify the clinical phenotype of CLN5 [91].

Conclusions

Twenty years after the identification of the first NCL genes, the pathophysiological pathways remain to be fully elucidated. The development of rational therapies for most forms of NCL is in the very early stages, and includes Phase I safety trials using gene therapy and stem cells to treat enzymatic forms (CLN1 and CLN2), and a Phase II trial of mycophenolate mofetil (Cellcept®) as an anti-inflammatory agent in the juvenile form/CLN3 (www.clinicaltrials.gov). Progress in identifying therapeutic targets has been hampered by the genotypic and phenotypic heterogeneity seen in the NCL disorders, as well as the lack of clear understanding of the functions of the NCL proteins. These proteins tend to be ubiquitously expressed, are possibly multifunctional proteins, and are enzymes whose substrates are mostly unknown or are difficult to study membrane proteins [16]. Nevertheless, the molecular discoveries in the recent years widen the opportunities for new research efforts aimed at detailed high-throughput biological profiling approaches (e.g. proteomics, lipidomics, and metabolomics) to advance knowledge of the NCL protein network and the pathways that are central to the disease process in the NCL disorders and related neurodegenerative diseases [92, 93]. Translation of these efforts will be greatly facilitated by more patient-oriented research efforts, such as improved access to patient samples (DNA, cell lines, and autopsy tissue) linked to clinical phenotype and genotype information (e.g. The NCL Mutation and Patient Database, www.ucl.ac.uk/ncl/mutation.shtml), biomarker development and natural history studies, as well as investigation of disease pathogenesis in human cell-based systems, such as those offered by cellular reprogramming to produce genotype-specific induced pluripotent stem cells (iPS cells).

Development of these human cell based systems will also greatly improve drug-screening efforts.

The recent discoveries in NCL genetics also underscore the notion that lysosomal storage analysis on tissue biopsy is an imperfect marker for NCL. If NCL-type storage material is found in multiple cell types in a patient with clinical symptoms of the disorder, a positive clinical NCL diagnosis can be made [1], but absence of storage material in rectal or skin punch biopsy or in peripheral blood lymphocytes cannot rule out the disease. In all cases, further definitive molecular diagnostic approaches should be undertaken, which may include measurement of enzymatic activity for PPT1 (*CLN1*) and TPP1 (*CLN2*), and sequencing and deletion/duplication analysis of NCL genes using traditional molecular methodologies. Next generation sequencing panels are also now available on a clinical basis and will target a variable number of well-known NCL mutations. Although bioinformatic analysis and interpretation is still challenging, clinical whole exome and whole genome sequencing are also now options for molecular diagnosis of simplex cases, or small clinically homogenous cohorts that remain molecularly unresolved. Results of these larger sequencing efforts will likely continue to extend the NCL genotypic and phenotypic spectrum.

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Figure 1. The broadening NCL biological pathway and genotypic and phenotypic spectrum
A. A hypothetical model of the expanding NCL biological pathway(s) is depicted. The genes mutated in NCL patients are indicated by boldface type and their putative protein cellular localizations are shown (*). The NCL proteins may function in common or intersecting pathways. Alternatively, one or more NCL proteins may function in parallel pathways that, when dysfunctional, lead to a shared pathology. Progranulin (GRN) and prosaposin (PSAP) similarly exist as both precursor polypeptides in the endoplasmic reticulum (ER) and in the secretory pathway (Golgi and transport vesicles [TV]) and extracellular space, and are cleaved into lower molecular weight peptides in the endosomal-lysosomal system. Lines on GRN and PSAP depict cleavage sites. GRN, PSAP, and cathepsin D (CTSD) are sorted within the secretory pathway and endosomal system via sortilin. CLN5 also binds sortilin/retromer complex. Ubiquitination (Ub) is an increasingly recognized mechanism for regulating trafficking in the endosomal-lysosomal system. Subunit c (SubC) and the saposins (SAPs), cleaved from PSAP, are the major proteins accumulating in NCL storage material within autophagic vacuoles (AV) and lysosomes (L). Subunit c is the pore-forming subunit of the mitochondrial ATP synthase complex (Complex V), and the SAPs are lipid carrying accessory proteins in the endosomal-lysosomal system. *indicates the protein localization; §indicates localization of the listed storage material. TV=transport vesicle; EE=early endosome; Ub=ubiquitin; LE=late endosome; MVB=multivesicular body; PAS=preautophagosomal structure; AP/AV=amphisome/autophagic vacuole; L=lysosome.
B. Venn diagram showing that new NCL genes (*GRN*, *ATP13A2*, and *KCTD7*) as well as

previously defined NCL genes (*TPP1*, *CLN6*, and *CLN8*) genes intersect with other neurodegenerative disorders. As described in the text, polymorphisms in the *CLN8* locus that influence its expression appear to be genetic modifiers of Gaucher disease. Other genes such as *POLG* and *TARDBP*, although not specifically identified as causative genes in NCL, may offer additional insight into NCL biology given their association with diseases showing clinicopathological overlap with NCL, including Parkinson's disease, mitochondrial disease, and frontotemporal lobar dementia (FTLD). *TARDBP* (*TAR DNA-binding protein 43*) encodes TDP-43, the protein that loses its nuclear localization and forms ubiquitinated, hyperphosphorylated inclusions in various forms of FTLD and amyotrophic lateral sclerosis (ALS). SCAR7, autosomal recessive spinocerebellar ataxia type 7.

Table 1

Genotype-phenotype correlations of the NCL disorder.

Disease	Prior designation	OMIM #	MI	Gene	Age of onset	Clinical phenotype	Early Symptoms and Signs	Usual survival	Pathology
CLN1	INCL	256730	AR	PPT1	6 - 24mos	classic infantile	developmental failure, seizures, myoclonus, visual failure	2 - 6 yrs	GROD
					2 - 4yrs	late-infantile	dev regression, seizures, visual failure	5 - 12+ yrs	
					4 - 6yrs	juvenile	visual failure, seizures, behavioral, dementia	10 - 20yrs	
CLN2	vLINCL	204500	AR	TPP1	2 - 4yrs	classic late infantile, [juvenile]	malignant seizures, myoclonus, developmental & visual failure	6 - 12+ yrs	CL
CLN3	JNCL (Batten)	204200	AR	CLN3	3 - 8yrs	classic juvenile	visual failure, dementia, behavioral and motor difficulties, late seizures	20 - 40yrs	Vacuolated lymphocytes, FP, CL, RL
CLN4	ANCL (Parry)	162350	AD	DNAJC5	teenage - 30+	juvenile to adult	dementia, seizures, myoclonus, without visual loss	5 - 20yrs	GROD
CLN5	vLINCL ¹	256731	AR	CLN5	3 - 7yrs	Variant late infantile, [juvenile, adult]	behavior abnl, cognitive decline, seizures, visual failure, myoclonus, motor difficulties	teenage+	CL, FP, RL
CLN6	vLINCL ²	601780	AR	CLN6	1.5 - 8yrs	Variant late infantile	visual failure, cognitive decline, seizures, myoclonus	teenage+	FP, CL
	ANCL Kufs, type A	204300			16 - 51 yrs	adult-onset	progressive myoclonic epilepsy, no retinal changes		FP, GROD
CLN7	vLINCL ³	610951	AR	MFSD8	1.5 - 6yrs	Variant late infantile, [juvenile, adult]	visual failure, dementia, seizures, myoclonus	teenage+	RL, FP
CLN8	vLINCL	600143	AR	CLN8	1.5 - 7yrs	variant late infantile	myoclonic seizures, visual failure, ataxia, cognitive decline	teenage+	GROD, CL [FP]
	EPMR	610003			5 - 10yrs	Northern epilepsy	seizures, slow dementia without visual loss	40+	GROD, CL
CLN10	CNCL	610127	AR	CTSD	neonatal	congenital [late infantile, adult]	Epileptic encephalopathy, microcephaly	< 1 yr	GROD
CLN11	FTLD-GRN	614706	AR	GRN	early 20s	adult	visual failure, myoclonic seizures, ataxia, dementia	30+	FP
		607485	AD		35 - 65yrs	adult	myoclonic seizures, ataxia, cognitive decline	50+	TDP-43
CLN12	Kufor-Rakeb syndrome	606693	AR	ATP13A2	8 - 12 yrs	juvenile	parkinsonism, ataxia, dementia	30+	FP, vacuolated lymphocytes, NBIA
CLN13	Kufs, type B		AR	CTSF	20 - 30yrs	adult	movement abnl (ataxia, tremor) and dementia, rare seizures		FP [brain]
CLN14	EPM3	611726	AR	KCTD7	<2 years	infantile	seizures, motor & speech regression, visual failure	teenage	FP, GROD

¹Variant initially described in a Finnish population and referred to as the Finnish variant.

²Formerly described as Lake-Cavanagh early-juvenile NCL variant and Indian-variant late-infantile NCL.

³Formerly also called Turkish variant.

OMIM: Online Mendelian Inheritance in Man (www.omim.org)

MI: Mode of inheritance

AR: autosomal recessive

AD: autosomal dominant

INCL: infantile NCL

LINCL: late-infantile NCL; vLINCL: variant LINCL

ANCL: adult NCL

CNCL: congenital NCL

EPMR: epilepsy, progressive, with mental retardation

EPM3: epilepsy, progressive myoclonic 3, with or without intracellular inclusions; mos: months
yrs: years

dev: developmental

abnl: abnormal

GRD: granular osmiophilic deposit

CL: curvilinear

FP: fingerprint

RL: rectilinear

NBIA: Neurodegeneration with brain iron accumulation