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Neuronal Ceroid-Lipofuscinoses – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Batten Disease

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Summary

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Clinical characteristics

The neuronal ceroid-lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders characterized by progressive intellectual and motor deterioration, seizures, and early death. Visual loss is a feature of most forms. Clinical phenotypes have been characterized traditionally according to the age of onset and order of appearance of clinical features into infantile, late-infantile, juvenile, adult, and Northern epilepsy (also known as progressive epilepsy with mental retardation [EPMR]). There is however genetic and allelic heterogeneity; a proposed new nomenclature and classification system has been developed to take into account both the responsible gene and the age at disease onset; for example, CLN1 disease, infantile onset and CLN1 disease, juvenile onset are both caused by pathogenic variants in *PPT1* but with differing age of onset.

The most prevalent NCLs are CLN3 disease, classic juvenile and CLN2 disease, classic late infantile (although prevalence varies by ethnicity and country of family origin):

CLN2 disease, classic late infantile. The first symptoms typically appear between age two and four years, usually starting with epilepsy, followed by regression of developmental milestones, myoclonic ataxia, and pyramidal signs. Visual impairment typically appears at age four to six years and rapidly progresses to light /dark awareness only. Life expectancy ranges from age six years to early teenage.

CLN3 disease, classic juvenile. Onset is usually between ages four and ten years. Rapidly progressing visual loss resulting in severe visual impairment within one to two years is often the first clinical sign. Epilepsy with

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generalized tonic-clonic seizures and/or complex-partial seizures typically appears around age ten years. Life expectancy ranges from the late teens to the 30s.

Other forms of NCL may present with behavior changes, epilepsy, visual impairment, or slowing of developmental progress and then loss of skills. The course may be extremely variable. Some genotype-phenotype information is available.

Diagnosis/testing

The diagnosis of an NCL is increasingly based on assay of enzyme activity and molecular genetic testing. In unusual cases diagnosis relies on electron microscopy (EM) of biopsied tissues. The diagnostic testing strategy in a proband depends on the age of onset. Pathogenic variants in thirteen genes — *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, *MFSD8, CLN8, CTSD, DNAJC5, CTSF, ATP13A2, GRN, KCTD7* — are known to cause NCL.

Management

Treatment of manifestations: Treatment is currently symptomatic and palliative only. Seizures, malnutrition, gastroesophageal reflux, pneumonia, sialorrhea, depression and anxiety, spasticity, Parkinsonian symptoms, and dystonia can be effectively managed. Antiepileptic drugs (AEDs) should be selected with caution. Benzodiazepines may help control seizures, anxiety, and spasticity. Trihexyphenydate may improve dystonia and sialorrhea. Individuals with swallowing problems may benefit from placement of a gastric (G) tube. Antidepressants and antipsychotic agents are sometimes indicated for those with CLN3 disease.

Surveillance: Routine medical management of children and young adults with complex neurodisability will be relevant to all those affected by NCL, and may include surveillance for swallowing difficulties and recurrent aspiration; radiograph surveillance of hip joints and spine; screening ECG for those with CLN3 disease who are older than age 16 years.

Agents/circumstances to avoid: Carbamazepine and phenytoin may increase seizure activity and myoclonus and result in clinical deterioration; lamotrigine may exacerbate seizures and myoclonus, especially in CLN2 disease.

Genetic counseling

The NCLs are inherited in an autosomal recessive manner with the exception of adult onset, which can be inherited in either an autosomal recessive or an autosomal dominant manner.

Autosomal recessive NCL. The parents of a child with an autosomal recessive form of NCL are obligate heterozygotes, and therefore carry one mutated allele. Heterozygotes have no symptoms. At conception, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives is possible if the pathogenic variants in the family are known.

Prenatal testing for pregnancies at increased risk is possible if the proband has documented deficient enzyme activity or if the pathogenic variant(s) have been identified in the family.

Diagnosis

Schulz et al [2013] provides a diagnostic algorithm for the neuronal ceroid-lipofuscinoses (NCLs).

Clinical Diagnosis

Clinically, the NCLs are characterized by the following (Table 1):

- Seizures

- Progressive deterioration of cognition (dementia)
- Motor function impairment (involuntary movements, myoclonus in younger children, ataxia, spasticity)
- Vision loss

The first presenting symptom may vary among NCL phenotypes, which are typically distinguished on the basis of age of onset and clinical manifestations. Unusual pathogenic variants in many, if not all, NCL-associated genes may result in a milder or more severe disease phenotype.

Table 1. NCL Phenotypes and Their Known Associated Genes

Phenotype		Phenotype by Gene and Onset			Presenting Findings [1]
		Proportion	Gene	Age of Onset	
Congenital		Minor	*CTSD*	Before or around birth	• Sz • Microcephaly
Infantile (INCL)		Major	*PPT1*	6-24 mos	• Cognitive/motor decline • ↓VA • Sz
		Rare	*KCTD7*		
Late-infantile (LINCL)	Classic	Major	*TPP1*	2-4 yrs	• Sz • Motor/cognitive decline • ↓VA
	Variant	Major in Finland; minor elsewhere	*CLN5*	4-7 yrs	• Cognitive/motor decline • Sz • ↓VA
		Minor	*CLN6*	18 mos - 8 yrs	• Cognitive/motor decline • Sz • ↓VA
		Minor	*MFSD8*		• Cognitive/motor decline • Sz • ↓VA
		Minor	*CLN8*	3-7.5 yrs	• Motor decline • Sz • ↓VA
		Rare	*CTSD*		
		Minor	*PPT1*		
Juvenile (JNCL)	Classic	Major	*CLN3*	4-10 yrs	• ↓VA • Sz • Cognitive/motor decline, neuropsychiatric
	Variant	Minor	*PPT1*		
		Rare	*TPP1*		
		Rare	CLN9 [2]		
		Rare	*ATP13A2*		
Northern epilepsy (progressive epilepsy with mental retardation [EPMR])		Major in Finland, rare elsewhere	*CLN8*	5-10 yrs	• Sz • Cognitive decline • Sometimes ↓VA
Adult (ANCL) (Kufs disease)		Rare	*CTSD, PPT1, CLN3, CLN5, CLN6, CTSF, GRN*	15-50 yrs	• Cognitive/motor decline • Sz (type A); behavior abnormalities (type B)

Table 1. continued from previous page.

Phenotype	Phenotype by Gene and Onset			Presenting Findings [1]
	Proportion	Gene	Age of Onset	
Adult (ANCL) (Parry disease); autosomal dominant	Unknown	*DNAJC5*		

1. Cognitive/motor decline, vision loss (↓VA), and seizures (Sz) are listed in the order in which they are most likely to occur in each phenotype.
2. Locus name; gene unknown

Testing

Histologic findings. Electron microscopy (EM) studies can be performed with 5-10 mL of heparinized whole blood (lymphocytes) or tissue biopsies (now usually of skin, but previously of conjunctiva or other tissues). EM studies (Table 2) remain essential in the non-classical NCL types, and show the presence of the following:

- Granular osmiophilic deposits (GROD) in CLN1 disease and CLN10/*CTSD* forms
- Predominantly curvilinear profiles (CVB) in CLN2 disease
- Fingerprint profiles (FP) in CLN3 disease
- Mixed-type inclusions (CVB, FP, and GROD) in CLN5, CLN6, MFSD8, CLN8, and other late-infantile and adult variant forms

Note: The appearance of the pathologic inclusions can depend on the tissue examined.

Enzyme activity. Three lysosomal enzymes (Table 2) have been identified as being deficient in the neuronal ceroid-lipofuscinoses in white blood cells, fibroblasts, and chorionic villi:

- **Palmitoyl-protein thioesterase 1 (PPT-1)** encoded by *PPT1.* A fluorimetric assay for PPT-1 based on the fluorochrome 4-methylumbelliferone detects significantly reduced PPT-1 activity in leukocytes, fibroblasts, lymphoblasts, amniotic fluid cells, or chorionic villi in forms of NCL caused by *PPT1* pathogenic variants [Voznyi et al 1999].
- **Tripeptidyl-peptidase 1 (TPP-1)** encoded by *TPP1*. Individuals with *TPP1* pathogenic variants usually have significantly reduced enzymatic activity in leukocytes, fibroblasts, amniotic fluid cells, or chorionic villi [Junaid et al 1999].
- **Cathepsin D (CTSD)** encoded by *CTSD*. Individuals with *CTSD* pathogenic variants usually have significantly reduced enzymatic activity in leukocytes or fibroblasts.

A carrier of a pathogenic variant in *PPT1*, *TPP1,* or *CTSD* typically has 50% of normal enzymatic activity in PPT-1 or TPP-1 or CTSD, respectively [Das et al 1998, Zhong et al 1998, Sleat et al 1999, Zhong et al 2000a].

Table 2. Electron Microscopic Findings and Enzyme Activity by NCL Genotype

Locus Name	Gene	Pathologic Diagnosis on EM [1]	Lymphocytes	Enyzme Activity
CLN1	*PPT1*	GROD	Not vacuolated	PPT-1 deficient
CLN2	*TPP1*	CVB	Not vacuolated	TPP-1 deficient

Table 2. continued from previous page.

Locus Name	Gene	Pathologic Diagnosis on EM [1]	Lymphocytes	Enyzme Activity
CLN3	*CLN3*	FP	Vacuolated	Not applicable
CLN4	*DNAJC5*	GROD, mixed [2]	Not vacuolated	
CLN5	*CLN5*	FP	Not vacuolated	
CLN6	*CLN6*	CVB, FP, RL	Not vacuolated	
CLN7	*MFSD8*	CVB, FP, RL	Not vacuolated	
CLN8	*CLN8*	CVB- or GROD-like structures	Not usually vacuolated	
CLN9	Unknown	GROD, CVB	Not vacuolated	Unknown; probably not applicable
CLN10	*CTSD*	GROD	Not vacuolated	CTSD deficient
CLN11	*GRN*	FP	Not vacuolated	Not applicable
CLN12	*ATP13A2*	GROD, Mixed	Not vacuolated	Not applicable
CLN13	*CTSF*	FP or none	Not vacuolated	CTSF-deficient
CLN14	*KCTD7*	GROD, FP	Not vacuolated	Not applicable

CVB = curvilinear profiles; EM = electron microscopy; FP = fingerprint profiles; GROD = granular osmophilic deposits; PPT-1 = palmitoyl-protein thioesterase 1; RL = rectilinear complex; TPP-1 = tripeptidyl peptidase 1
1. In individuals with adult-onset disease, peripheral storage by EM may not be detected.
2. Mixed = CVB, FP, RL, GROD

Molecular Genetic Testing

Genes. *PPT1*, *TPP1*, *CLN3*, *DNAJC5, CLN5*, *CLN6*, *CLN7/MFSD8, CLN8, CTSD, GRN, ATP13A2, CTSF, KCTD7* are the genes in which pathogenic variants are known to cause the neuronal ceroid-lipofuscinoses.

Evidence for locus heterogeneity: CLN9. The gene has not been identified in the families assigned this locus.

Table 3. Molecular Genetic Testing Used in NCL

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Gene and Method [3]
PPT1	Targeted analysis for pathogenic variants	p.Arg122Trp [4]	Finnish: 98% [5]; Non-Finnish: 10% [6] for the targeted variant
		p.Arg151Ter [4]	60% [6] for the targeted variant
	Sequence analysis [6]	Sequence variants	>98% [7]
	Deletion/duplication analysis [8]	Exon & whole-gene deletions	Not known
TPP1	Targeted analysis for pathogenic variants	c.509-1G>C, p.Arg208Ter [4]	60%-90% [9] for the targeted variant
	Sequence analysis [6]	Sequence variants	97% [9]
CLN3	Targeted analysis for pathogenic variants	c.461-280_677+382del [10] (1-kb deletion)	96% [11] for the targeted c.461-280_677+382del deletion
	Sequence analysis [6]	Sequence variants	>98% [11]
DNAJC5	Sequence analysis [6]	Sequence variants	Not known, estimate >95%

Table 3. continued from previous page.

Gene [1]	Method	Variants Detected [2]	Variant Detection Frequency by Gene and Method [3]
CLN5	Targeted analysis for pathogenic variants	p.Tyr392Ter	94% (Finnish ancestry) [12]
	Sequence analysis [6]	Sequence variants	Est. 90%-95%
	Deletion/duplication analysis [8]	Exon & whole-gene deletions	Not known
CLN6	Sequence analysis [6]	Sequence variants	92% [13]
	Deletion/duplication analysis [8]	Exon & whole-gene deletions	Not known
MFSD8	Sequence analysis [6]	Sequence variants	Not known, ~ >95%
CLN8	Targeted analysis for pathogenic variants	p.Arg24Gly	~100% (Finnish ancestry) [14]
	Sequence analysis [6]	Sequence variants	Est. 90%-95%
	Deletion/duplication analysis [8]	Exon & whole-gene deletions	Not known
CTSD	Sequence analysis [6]	Sequence variants	Not known, est. >95%
GRN	Sequence analysis [6]	Sequence variants	Not known, est. >95%
ATP13A2	Sequence analysis [6]	Sequence variants	Not known, est. >95%
CTSF	Sequence analysis [6]	Sequence variants	Not known, est. >95%
KCTD7	Sequence analysis [6]	Sequence variants	Not known, est. >95%

See Table 1 for phenotypes associated with pathogenic variants in each gene.
1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene: % of individuals with at least one identifiable variant
4. Pathogenic variant(s) included in targeted analysis may vary among laboratories.
5. PPT-1 enzyme-deficient individuals with INCL [Bellizzi et al 2000]
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. PPT-1 enzyme-deficient individuals [Das et al 1998, Hofmann et al 1999]
8. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
9. TPP-1 enzyme-deficient individuals with LINCL [Zhong et al 1998, Hartikainen et al 1999, Lauronen et al 1999, Sleat et al 1999, Zhong et al 2000b]
10. Common deletion of exons 7 and 8 (see Molecular Genetics)
11. Individuals with JNCL [Munroe et al 1997, Mao et al 2003, Mole et al 2004, Leman et al 2005]
12. Individuals of Finnish ancestry have variant LINCL and the *CLN5* pathogenic variant (p.Tyr392Ter) [Savukoski et al 1998]
13. Families with vLINCL with linkage to *CLN6* [Gao et al 2002, Sharp et al 2003, Teixeira et al 2003]
14. For individuals of Finnish ancestry [Ranta et al 2001, Ranta et al 2004]

Testing Strategy

The testing strategy to confirm/establish the diagnosis in a proband depends on the age of onset, and is summarized in Table 4.

If EM indicates typical NCL storage material, all NCL-related genes may eventually need to be tested by enzymatic activity or by sequencing.

Table 4. Diagnostic Algorithm for NCL Diseases

Clinical Presentation	Diagnostic Algorithm		Gene(s) for which Molecular Genetic Testing Should be Considered
Newborn w/epilepsy & microcephaly	Enzyme testing for CTSD (leukocytes or fibroblasts)	If CTSD deficient:	*CTSD*
	If CTSD enzyme activity is normal, consider enzyme assay for PPT-1 & TPP-1.	If PPT-1 deficient:	*PPT1*
		If TPP-1 deficient:	*TPP1*
Young child (>6 mos) w/ developmental standstill or regression &/or newly occurring severe epilepsy of unknown cause	Enzyme testing for PPT-1 & TPP-1 (dry blood spots or leukocytes or fibroblasts)	If PPT-1 deficient:	*PPT1*
		If TPP-1 deficient:	*TPP1*
	If PPT-1 & TPP-1 enzyme activities are normal, EM exam (skin biopsy or lymphocytes)	If storage material is present:	*CLN5, CLN6, MFSD8, CLN8, KCTD7*
School child w/visual loss &/or dementia & epilepsy	Search for lymphocyte vacuoles (light microscopy of blood smear).	If lymphocyte vacuoles are present:	*CLN3*
	If no lymphocyte vacuoles, enzyme testing for PPT-1, TPP-1, & CTSD	If PPT-1 deficient:	*PPT1*
		If TPP-1 deficient:	*TPP1*
		If CTSD deficient:	*CTSD*
	If PPT-1 and TPP-1 enzyme activities are normal, EM exam (skin biopsy or lymphocytes)	If storage material is present:	*CLN5, CLN6, MFSD8, CLN8, ATP13A2*
Young adult w/nonspecific mental, motor, or behavioral abnormalities	Enzyme testing for PPT-1, TPP-1, CTSD, & CTSF	If PPT-1 deficient:	*PPT1*
		If TPP-1 deficient:	*TPP1*
		If CTSD deficient:	*CTSD*
		If CTSF deficient:	*CTSF*
	• If enzyme activities are normal, EM exam (skin biopsy or lymphocytes) • If storage material is present, genetic testing (eventually in special cases even w/out detection of storage material); consider possible MOI.	If autosomal dominant:	*DNAJC5*
		If autosomal recessive:	*CLN6*, *GRN*, *CTSF*

EM = electron microscopic; MOI = mode of inheritance
Adapted from Schulz et al [2013]; reprinted with permission from Elsevier

Carrier testing for relatives at risk for the autosomal recessive forms of NCL requires prior identification of the pathogenic variants in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant(s) in the family.

Enzymatically or genetically undefined cases. Store DNA and fibroblast cell lines and consult an NCL research scientist who may be able to access new research tests, or store samples until diagnostic tests become available.

Note: Cell banking is the storage of cell lines (typically derived from a skin biopsy) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking cells particularly when all of the genes responsible have not yet been identified, not all pathogenic variants have been elucidated, or testing is available on a research or linkage basis only. These cells can also be used to supply unlimited DNA or RNA samples.

Clinical Characteristics

Clinical Description

All individuals with a neuronal ceroid-lipofuscinosis (NCL) have progressive decline, an evolving cognitive and motor disorder, and seizures. With the exception of adult neuronal ceroid-lipofuscinosis (ANCL) and Northern epilepsy (NE), NCL phenotypes are usually associated with progressive loss of vision.

A direct correlation between the gene that is mutated and phenotype does not always exist (see Table 1 and Genotype-Phenotype Correlations); for example, individuals with pathogenic variants in *PPT1* can present with four different phenotypes (infantile, late-infantile, juvenile, and adult onset). Nonetheless, describing the NCLs by clinical phenotype is useful for medical management and prognosis [Das et al 1998, Wiśniewski et al 1998a, Wiśniewski et al 1999, van Diggelen et al 2001, Wiśniewski et al 2001].

CLN1 Disease, Classic Infantile (previously Classic Infantile NCL, INCL, Santavuori-Haltia)

CLN1 disease usually presents between age six and 24 months. Onset before age six months and after age two years also occurs [Das et al 1998, Wiśniewski et al 1998a, Wiśniewski et al 1999, van Diggelen et al 2001, Wiśniewski et al 2001].

Initial signs include: delayed development, myoclonic jerks, and/or seizures. In one series of 21 affected children, early signs were deceleration of head growth and specific electroencephalographic (EEG) changes (from age 13 months). Hand stereotypies resembling those seen in Rett syndrome are recognized. In a study of eight newly diagnosed children with INCL (ages 15-27 months), mild-to-moderate deterioration of intellectual ability was observed in all [Riikonen et al 2000]. The children had speech problems and lost interest in playing and in toys, but remained interested in their surroundings. They had moderate motor dysfunction.

Retinal blindness and seizures are evident by age two years. The ERG (electroretinogram) is unrecordable by age four years.

Psychomotor abilities deteriorate rapidly. Life expectancy varies from age two to nine years.

MRI findings are: variable cerebral atrophy; signal change in the thalami and basal ganglia; and thin, hyperintense, periventricular high-signal rims of white matter [Riikonen et al 2000]. The progressive diffuse brain atrophy on MRI seen in children with INCL during the first four years of life then stabilizes.

CLN2 Disease, Classic Late Infantile (previously Late-Infantile NCL, LINCL, Jansky-Bielschowsky Disease)

The first symptoms of CLN2 disease typically appear between age two and four years, usually starting with epilepsy. Generalized tonic-clonic seizures, absences, and partial-onset seizures may be observed. Myoclonus becomes prominent after the onset of seizures. Sometimes slowing of developmental milestones is evident before

the onset of seizures. Following the onset of seizures, previously acquired motor/language and cognitive skills are lost.

Visual impairment appears between age four and six years and rapidly progresses to blindness.

Affected children are usually bedridden by age six years; disabilities are severe and nursing care needs are considerable by mid-childhood. Life expectancy is between age six years and adolescence but can be longer [Wiśniewski et al 1998a, Wiśniewski et al 1999].

Early electroencephalogram (EEG) may show spikes in the occipital region in response to photic stimulation at 1-2 Hz. Electroretinogram (ERG) is usually abnormal at presentation and becomes undetectable soon thereafter. On occasion, the ERG may be normal at presentation [Weleber 1998].

Visual evoked potentials (VEPs) are enhanced for a long period and diminish in the final stage of the disease.

MRI shows progressive cerebellar and cerebral atrophy with normal basal ganglia and thalami.

Variants of late-infantile NCL. Many variant types are caused by pathogenic variants in distinct genes (Table 1). Some variant types are associated with but not exclusive to certain ethnic origins.

The clinical features of variant late-infantile NCL types may have typical characteristics, but in general overlap:

- **CLN5 disease, variant late infantile.** The onset of disease is usually ages 4.5 to seven years in Finland. Life expectancy is between 13 and 35 years.
- **CLN6 disease.** Visual loss and seizures may be the initial signs and symptoms. In children with onset after age four years, epilepsy, ataxia, and myoclonus may be the initial features.
- **MFSD8/CLN7 disease.** Visual loss and seizures may be the initial signs and symptoms. In children with onset after age four years, epilepsy, ataxia, and myoclonus may be the initial features.
- **CLN8 disease.** Onset may be earlier, between age two and six years [Sharp et al 2003].
- **Genetically undefined**

CLN3 Disease (previously Classic Juvenile NCL, JNCL, Batten Disease, Spielmeyer-Vogt Disease)

Onset is usually between age four and eight years (mean age ~5 years).

Rapidly progressing vision loss is almost always the first clinical sign of the disease and may be the only sign for two to five years. Children become severely visually impaired within two to four years of the onset of vision loss. Ophthalmologic examination early in the course of JNCL may reveal macular changes only; gradually, typical signs of pan-retinal degeneration develop: pigmentary changes in the retinal periphery, vascular attenuation, and optic nerve pallor. ERG shows loss of photoreceptor function early on [Weleber 1998].

Epilepsy with generalized tonic-clonic seizures and/or focal-onset seizures typically appears between age nine and 18 years. The EEG shows nonspecific disorganization and spike-and-slow-wave complexes.

Little variation is observed in the visual symptoms and seizures, but variation can occur in the progression of motor and intellectual deterioration. Speech disturbances (festinating stuttering, often mislabeled as echolalia) and slow decline in cognition occur around the time of onset of seizures.

Behavioral problems, extrapyramidal signs, and sleep disturbance occur in the second decade. Bäckman et al [2005] found that some individuals with JNCL experience multiple psychiatric problems including disturbed thoughts, attention problems, somatic complaints, and aggressive behavior. Depression was uncommon.

There is recent evidence of cardiac involvement late in the disease: progressive cardiac involvement with repolarization disturbances, ventricular hypertrophy, and sinus node dysfunction [Ostergaard et al 2011].

Most individuals with CLN3 disease live until the late teens or early 20s; some may live into their 30s.

CT and MRI reveal cerebral, and to a lesser degree, cerebellar atrophy in the later stages (age >15 years).

Atypical JNCL. Individuals with atypical JNCL are often compound heterozygotes for *CLN3* pathogenic variants (c.461-280_677+382del and another pathogenic variant). For example, p.Glu295Lys is associated with a particularly protracted disease in which a high level of functioning can be maintained for several decades. In other examples onset of epilepsy was delayed for a decade or more. The cause of these phenotypic differences is unknown. All types with pathogenic variants in *CLN3* have visual failure but vary in the severity of seizures and other neurologic complications.

JNCL variants are also caused by milder pathogenic variants in genes that usually cause a more severe NCL, in particular *CLN1*.

JNCL variant – CLN9. Two families in which the underlying gene is not known have been described [Schulz et al 2004].

Adult NCL (ANCL)

Initial signs and symptoms usually appear around age 30 years, with death occurring about ten years later. Symptoms may appear as early as age 11 years or much later in adulthood. Ophthalmologic studies are normal.

The two major clinical phenotypes are:

- **Type A,** characterized by progressive myoclonic epilepsy with dementia, ataxia, and late-occurring pyramidal and extrapyramidal signs. Seizures are often uncontrollable. Individuals with this type have been found to have pathogenic variants in *CLN6;* it is now known as adult CLN6 disease.
- **Type B,** characterized by behavior abnormalities and dementia, which may be associated with motor dysfunction, ataxia, extrapyramidal signs, and suprabulbar (brain stem) signs. Some families have been found to have pathogenic variants in *CTSF*.

In the presenile form with onset after age 50 years, dementia, cognitive decline, motor dysfunction, seizures, and suprabulbar signs are observed as well as mixed inclusions on EM (Table 2).

Autosomal dominant forms of adult-onset NCL have GROD observed on EM (Table 2) [Burneo et al 2003, Nijssen et al 2003], with some having pathogenic variants in *DNAJC5*. The genetically defined cases of recessive adult-onset NCL include several individuals with deficient PPT-1 enzyme activity [van Diggelen et al 2001, Ramadan et al 2007], deficient CTSD enzyme activity [Author, unpublished], or pathogenic variants in *CLN5*. Adult-onset disease, previously known as Kufs disease type A, results from pathogenic variants in *CLN6* [Arsov et al 2011]; some cases of Kufs disease type B result from reduced CTSF activity [Smith et al 2013]. It is highly likely that a mild pathogenic variant in all known NCL-associated genes could delay disease onset until adulthood.

Northern Epilepsy (NE, Progressive Epilepsy with Mental Retardation, EPMR)

Northern epilepsy is a specific phenotype caused by a particular pathogenic variant in *CLN8*, and is characterized by epilepsy with tonic-clonic or complex-partial seizures, slow intellectual deterioration, and motor dysfunction.

Vision problems are rare.

The frequency of the epileptic manifestations decreases after puberty, but slow cognitive decline continues throughout life. Some individuals have lived beyond age 60 years.

Genotype-Phenotype Correlations

Mutation of the following NCL-related genes can be associated with both early and late age of onset – the latter probably the result of greater amounts of residual protein activity:

- **CLN10/*CTSD*.** Congenital, late-infantile, or teenage-/adult-onset NCL
- **CLN1/*PPT1*.** Infantile, late-infantile, juvenile, and adult-onset NCL
- **CLN2/*TPP1*.** Late-infantile, juvenile, and possibly later-onset NCL
- ***CLN5*.** Late-infantile variant, juvenile, and adult-onset NCL
- ***CLN6*.** Late-infantile variant, and adult-onset NCL
- ***CLN8*.** Late-infantile variant NCL and EPMR

Later ages of onset have not yet been described for *CLN3* or *CLN7*/*MFSD8*.

Nomenclature

Neuronal ceroid-lipofuscinoses nomenclature is now gene based [Williams & Mole 2012].

Table 5. Former NCL Nomenclature

Eponym	Disease	OMIM	Clinical Phenotype	Former Abbreviated Name
Haltia-Santavuori	CLN1	256730	Infantile classic	INCL
Janský-Bielschowsky	CLN2	204500	Late-infantile classic	LINCL
Spielmeyer-Sjögren	CLN3	204200	Juvenile	JNCL
Kufs type A	CLN6	204300	Adult	ANCL
Kufs type B	CLN13		Adult	ANCL
Finnish variant late infantile	CLN5	256731	Late-infantile variant	vLINCL
Lake-Cavanagh or Indian variant late infantile	CLN6	601780	Early-juvenile variant & late-infantile variant	vLINCL
Turkish variant late infantile	CLN7	610951	Late-infantile variant	vLINCL
Northern epilepsy/EPMR	CLN8	600143	EPMR, late-infantile variant	vLINCL
Parry	CLN4	162350	Adult autosomal dominant	ANCL

Adapted from Williams & Mole [2012]

Batten disease was originally used to refer only to what is now known to be classic CLN3 disease. However, more recently it is being used to provide an accessible name for all types of NCL, regardless of genetic alteration.

Incidence and Prevalence

Neuronal ceroid-lipofuscinoses (NCLs) are the most common hereditary progressive neurodegenerative disease with a prevalence of approximately 1.5 to nine per million population [Mole et al 2011].

The incidence of NCL ranges in different countries from 1.3 to seven per 100,000 live births [Mole et al 2011].

Genetically Related (Allelic) Disorders

***CTSD*, *PPT1*, *TPP1*, *DNAJC5*, *CLN5*, *CLN6*, *MFSD8*, or *CLN8*.** No other phenotypes are associated with pathogenic variants in these genes.

***ATP13A2*.** Pathogenic variants in *ATP13A2* may also be associated with Kufor-Rakeb syndrome.

GRN. Heterozygous pathogenic variants in *GRN* may also be associated with frontotemporal lobar degeneration with TDP43 inclusions.

KCTD7. Pathogenic variants in *KCTD7* may also be associated with progressive myoclonic epilepsy type 3 (EPM3).

CLN3. It is a possible that different phenotypes are associated with pathogenic variants other than the 1-kb deletion in *CLN3* [Kitzmüller et al 2008].

Differential Diagnosis

In a UK epidemiologic study of progressive intellectual and neurologic deterioration over 12 years, 147 different diagnoses were recorded in 1114 of 2636 patients younger than age 16 years. The six most common groups of disorders were leukoencephalopathies (183 cases), neuronal ceroid-lipofuscinoses (141), mitochondrial disorders (122), mucopolysaccharidoses (102), gangliosidoses (100), and peroxisomal disorders (69) [Verity et al 2010].

CLN1 disease. Other progressive neurologic diseases with onset from birth to age two years need to be considered. These include: hexosaminidase A deficiency, progressive leukodystrophies Rett syndrome, peroxisomal biogenesis disorders, Neimann-Pick disease types A and B (see Acid Sphingomyelinase Deficiency), and Leigh syndrome (see also Mitochondrial Disorders Overview). While some of these disorders are associated with cortical blindness, retinal involvement is rarely seen.

CLN2 disease. Other progressive neurologic diseases with onset from ages two to four years need to be considered. These include: epileptic encephalopathies, other lysosomal storage disorders, mitochondrial disease, and leukodystrophies.

CLN3 disease. In the initial stage when individuals present with visual loss, retinitis pigmentosa (RP) or cone-rod dystrophy may be considered. The ophthalmologic involvement of JNCL differs from classic RP in that the vision loss in CLN3 disease is typically central at first (rather than peripheral) and rapidly progressive, with total blindness occurring in one to two years [Weleber 1998]. In contrast, RP is indolent and progresses slowly over decades. Other disorders in which a cone-rod retinal dystrophy occurs are: Bardet-Biedl syndrome, Joubert syndrome, juvenile nephronophthisis, and Alstrom syndrome, all of which can be distinguished from CLN3 disease by their clinical features.

Northern epilepsy (NE) needs to be distinguished from other neurologic conditions with seizures [Zupanc & Legros 2004]. Myoclonus is not a feature of NE, and thus a large number of disorders with myoclonic seizures and intellectual disability can be excluded. The clinical course of NE differs from Landau-Kleffner syndrome, Rasmussen syndrome, and epilepsy with electric status epilepticus during slow sleep. Tuberous sclerosis complex and the Sturge-Weber syndrome can be distinguished from NE on the basis of clinical and neuroradiologic features. Lack of pyramidal or extrapyramidal signs and lack of cerebellar ataxia distinguish NE from degenerative disorders such as: juvenile Huntington disease, PKAN (previously called Hallervorden-Spatz syndrome), juvenile GM2 gangliosidosis (see Hexosaminidase A Deficiency), Niemann-Pick disease type C, giant axonal neuropathy, or neuronal intranuclear inclusion disease (OMIM 603472).

Adult Kuf's disease. The differential diagnosis includes progressive myoclonic epilepsies (see Lafora Progressive Myoclonus Epilepsy), Unverricht-Lundborg disease, mitochondrial disease including MERRF (see also Mitochondrial Disease Overview); early-onset dementias, Creutzfeldt-Jakob Disease (CJD), and dentatorubral-pallidoluysian atrophy (DRPLA).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with one of the neuronal ceroid-lipofuscinoses, the following evaluations are recommended:

- Neurologic examination
- Ophthalmologic examination
- Developmental/cognitive and educational assessment
- Clinical genetics consultation

Treatment of Manifestations

Symptomatic treatment can be successful in mitigating the manifestations of NCL. Seizures, sleep-related problems, malnutrition, gastroesophageal reflux, pneumonia, sialorrhea, hyperactivity and behavior problems, psychosis, anxiety, spasticity, Parkinsonian symptoms, and dystonia can be palliated.

Seizures. Antiepileptic drugs (AEDs) should be selected with caution. The stage of the disease, age of the affected individual, and quality of life are important to consider in evaluating the effectiveness of AEDs.

Lamotrigine (LTG) had a favorable effect on 23/28 individuals with JNCL, 13/19 being continued on monotherapy with 100% control, compared to 70% control for those receiving valproic acid (VPA), 60% control for VPA-clonazepam (CZP), and 60% control for LTG-CZP [Aberg et al 1999, Aberg et al 2000].

Other newer AEDs including levetiracetam and topiramate may also be beneficial [Author, personal experience].

Other. Benzodiazepines may be of benefit for seizures, anxiety, spasticity, and sleep disorders.

Trihexyphenydil improves dystonia and sialorrhea.

Individuals with swallowing problems may benefit from placement of a gastric (G) tube.

Antidepressants and antipsychotic agents are sometimes indicated for those with CLN3 disease.

Surveillance

Routine medical management of children and young adults with complex neurodisability will be relevant to all those affected by NCL. This may include clinical surveillance for the following:

- Swallowing difficulties and recurrent aspiration
- X-ray surveillance of hip joints and spine
- Screening ECG for those individuals with CLN3 disease who are older than age 16 years

Agents/Circumstances to Avoid

Carbamazepine (CZP) and phenytoin may increase seizure activity and myoclonus in NCL and result in clinical deterioration.

Lamotrigine may exacerbate seizures and myoclonus especially in CLN2 disease.

In a series of 60 individuals with JNCL, valproic acid (VPA) was withdrawn in 20% and clonazepam (CZP) in 16% because of side effects [Aberg et al 2000].

- Fifty percent of individuals receiving VPA had sleep disturbances or excessive sedation.

- CZP stimulates salivation and respiratory secretions, increasing the risk for pneumonia in bedridden individuals, many of whom have gastroesophageal reflux. CZP is a sedative and can cause behavior disturbances.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Crystal et al [2004] initiated gene therapy for children with LINCL caused by pathogenic variants in *CLN2*. They administered a replication-deficient adeno-associated virus (AAV) vector expressing human *CLN2* cDNA directly into the brains of children with either severe or moderate LINCL in an attempt to produce sufficient amounts of TPP-1, to prevent further loss of neurons and hence limit disease progression. The research is ongoing.

Stem cell therapy for phenotypes caused by pathogenic variants in *CLN1* and *CLN2* is in progress [Author, personal communication].

The drug EGIS-8332, which targets AMPA receptors, improved performance in a CLN3 disease mouse model. Trials in humans have not yet started. Talampanel (LY300164) is a drug which targets the same receptors and is being assessed in a clinical trial to treat epilepsy and Parkinson disease in humans. Plans to test this drug in a mouse model for CLN3 disease are underway at the University of Rochester Medical Center (Rochester, New York, USA).

The University of Rochester Medical Center is also conducting a clinical trial using the immunosuppressant mycophenolate (mycophenolate mofetil, Cellcept®, Myfortic®, mycophenolate sodium or mycophenolic acid) in individuals with juvenile CLN3.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The NCLs are inherited in an autosomal recessive manner with the exception of adult NCL, which can be inherited in either an autosomal recessive or an autosomal dominant manner.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutated allele). Obtaining parental samples to confirm carrier status is recommended once pathogenic variants have been identified in the proband.

- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

Offspring of a proband

- Probands with INCL, LINCL, and classic JNCL do not reproduce.
- Very rarely, individuals with atypical JNCL reproduce [Wiśniewski et al 1998b]. The offspring of an individual with NCL are obligate heterozygotes (carriers) for a mutated allele causing NCL.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Carrier testing by DNA analysis is possible once the pathogenic variants in the underlying gene have been identified in the family.

Autosomal Dominant Inheritance (adult NCL only) – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant adult NCL have an affected parent.
- A proband with autosomal dominant adult NCL may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- If the pathogenic variant found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing of the identified variant. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with autosomal dominant adult NCL have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- The sibs of a proband with clinically unaffected parents are still at increased risk (for the disorder) because of the possibility of reduced penetrance in a parent.
- If the pathogenic variant found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant adult NCL has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

If biochemical studies in the proband have revealed deficient activity of the enzyme CTSD, PPT-1, or the enzyme TPP-1, or if the pathogenic variant(s) have been identified in the proband and parents, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Batten Disease Family Association (BFDA)**
  c/o Heather House
  Heather Drive
  Tadley Hampshire RG26 4QR
  United Kingdom
  Phone: 01603 760111; 01233 639526
  Email: info@bdfa-uk.org.uk; support@bdfa-uk.org.uk
  www.bdfa-uk.org.uk

- **Batten Disease Support and Research Association (BDSRA)**
  1175 Dublin Road
  Columbus OH 43215
  Phone: 800-448-4570 (toll-free)
  Email: info@bdsra.org
  www.bdsra.org

- **Charlotte and Gwenyth Gray Foundation to Cure Batten Disease**
  6033 West Century Boulevard
  Suite 350
  Los Angeles CA 90045
  Phone: 310-649-5222

Email: curebatten@givingback.org
www.curebatten.org

- **NCL Resource - A Gateway for Batten Disease**
  MRC Laboratory for Molecular Cell Biology, University College London
  Gower Street
  London WC1E 6BT
  United Kingdom
  Phone: +00 44 207 679 7257
  Email: ncl-www@ucl.ac.uk
  www.ucl.ac.uk/ncl

- **Children's Brain Disease Foundation**
  Parnassus Heights Medical Building
  350 Parnassus Avenue
  Suite 900
  San Francisco CA 94117
  Phone: 415-665-3003
  Fax: 415-665-3003
  Email: jrider6022@aol.com

- **Metabolic Support UK**
  5 Hilliards Court, Sandpiper Way
  Chester Business Park
  Chester CH4 9QP
  United Kingdom
  Phone: 0845 241 2173
  Email: contact@metabolicsupportuk.org
  www.metabolicsupportuk.org

- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  2001 Beacon Street
  Suite 204
  Boston MA 02135
  Phone: 800-906-8723 (toll-free)
  Fax: 617-277-0134
  Email: info@ntsad.org
  www.ntsad.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Neuronal Ceroid-Lipofuscinoses: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CLN1	*PPT1*	1p34.2	Palmitoyl-protein thioesterase 1	Retina International Mutations of the Palmitoyl-Protein Thioesterase Gene (PPT CLN1) Gene (PPT1) Neuronal Ceroid Lipofuscinoses; NCL Mutations (PPT1) PPT1 database	PPT1	PPT1
CLN2	*TPP1*	11p15.4	Tripeptidyl-peptidase 1	Neuronal Ceroid Lipofuscinoses; NCL Mutations (TPP1) TPP1 database	TPP1	TPP1
CLN3	*CLN3*	16p12.1	Battenin	Retina International Mutations of the CLN3 Gene Neuronal Ceroid Lipofuscinoses; NCL Mutations (CLN3) CLN3 database	CLN3	CLN3
CLN4	*DNAJC5*	20q13.33	DnaJ homolog subfamily C member 5	DNAJC5 @ LOVD Neuronal Ceroid Lipofuscinoses; NCL Mutations (DNAJC5)	DNAJC5	DNAJC5
CLN5	*CLN5*	13q22.3	Ceroid-lipofuscinosis neuronal protein 5	Neuronal Ceroid Lipofuscinoses; NCL Mutations (CLN5) CLN5 database	CLN5	CLN5
CLN6	*CLN6*	15q23	Ceroid-lipofuscinosis neuronal protein 6	Neuronal Ceroid Lipofuscinoses; NCL Mutations (CLN6) CLN6 database	CLN6	CLN6
CLN7	*MFSD8*	4q28.2	Major facilitator superfamily domain-containing protein 8	Neuronal Ceroid Lipofuscinoses; NCL Mutations (MFSD8) MFSD8 database	MFSD8	MFSD8
CLN8	*CLN8*	8p23.3	Protein CLN8	Neuronal Ceroid Lipofuscinoses; NCL Mutations (CLN8) CLN8 database	CLN8	CLN8
CLN9	Unknown	Unknown				
CLN10	*CTSD*	11p15.5	Cathepsin D	Neuronal Ceroid Lipofuscinoses; NCL Mutations (CTSD) CTSD database	CTSD	CTSD
CLN11	*GRN*	17q21.31	Progranulin	Alzheimer Disease & Frontotemporal Dementia Mutation Database (GRN) Neuronal Ceroid Lipofuscinoses; NCL Mutations (GRN) GRN database	GRN	GRN
CLN12	*ATP13A2*	1p36.13	Cation-transporting ATPase 13A2	ATP13A2 @ LOVD	ATP13A2	ATP13A2
CLN13	*CTSF*	11q13.2	Cathepsin F	Neuronal Ceroid Lipofuscinoses; NCL Mutations (CTSF) CTSF @ LOVD	CTSF	CTSF
CLN14	*KCTD7*	7q11.21	BTB/POZ domain-containing protein KCTD7	Neuronal Ceroid Lipofuscinoses; NCL Mutations (KCTD7) KCTD7 database	KCTD7	KCTD7

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Neuronal Ceroid-Lipofuscinoses (View All in OMIM)

116840	CATHEPSIN D; CTSD
138945	GRANULIN PRECURSOR; GRN
162350	CEROID LIPOFUSCINOSIS, NEURONAL, 4B, AUTOSOMAL DOMINANT; CLN4B
204200	CEROID LIPOFUSCINOSIS, NEURONAL, 3; CLN3
204300	CEROID LIPOFUSCINOSIS, NEURONAL, 4A, AUTOSOMAL RECESSIVE; CLN4A
204500	CEROID LIPOFUSCINOSIS, NEURONAL, 2; CLN2
256730	CEROID LIPOFUSCINOSIS, NEURONAL, 1; CLN1
256731	CEROID LIPOFUSCINOSIS, NEURONAL, 5; CLN5
600143	CEROID LIPOFUSCINOSIS, NEURONAL, 8; CLN8
600722	PALMITOYL-PROTEIN THIOESTERASE 1; PPT1
601780	CEROID LIPOFUSCINOSIS, NEURONAL, 6; CLN6
603539	CATHEPSIN F; CTSF
606725	CLN6 GENE; CLN6
607042	CLN3 GENE; CLN3
607837	CLN8 GENE; CLN8
607998	TRIPEPTIDYL PEPTIDASE I; TPP1
608102	CLN5 GENE; CLN5
609055	CEROID LIPOFUSCINOSIS, NEURONAL, 9; CLN9
610127	CEROID LIPOFUSCINOSIS, NEURONAL, 10; CLN10
610513	ATPase, TYPE 13A2; ATP13A2
610951	CEROID LIPOFUSCINOSIS, NEURONAL, 7; CLN7
611124	MAJOR FACILITATOR SUPERFAMILY DOMAIN-CONTAINING PROTEIN 8; MFSD8
611203	DNAJ/HSP40 HOMOLOG, SUBFAMILY C, MEMBER 5; DNAJC5
611725	POTASSIUM CHANNEL TETRAMERIZATION DOMAIN-CONTAINING PROTEIN 7; KCTD7
611726	EPILEPSY, PROGRESSIVE MYOCLONIC, 3, WITH OR WITHOUT INTRACELLULAR INCLUSIONS; EPM3
614706	CEROID LIPOFUSCINOSIS, NEURONAL, 11; CLN11

Molecular Pathogenesis

Both human and animal forms of neuronal ceroid-lipofuscinoses can be divided into two major groups, based on the nature of the material accumulated in lysosomes:

- Those characterized by the prominent storage of saposins (SAPs) A and D; and
- Those showing the predominance of subunit c of mitochondrial ATP synthase accumulation.

In addition to proteins, storage material in NCLs contains other components including lipids, metals, dolichyl pyrophosphoryl oligosaccharides, and lipid thioesters.

The relation between genetic defects associated with the major NCL forms, the accumulation of storage material, and tissue dysfunction and/or damage is still unknown. Furthermore, all individuals with NCLs manifest lysosomal storage in many tissues and organs, but severe degeneration and cell loss involve mostly neuronal cells. Thus, it appears that NCL proteins may be most critical for the metabolism of neurons. It is uncertain

whether this phenomenon results from the specific metabolic requirements of a neuron as a postmitotic cell, or from the properties of NCL proteins per se.

The spectrum of pathogenic variants present in NCL is listed in the NCL Mutation Database www.ucl.ac.uk/ncl (see also Table A).

For a detailed summary of gene and protein information for the genes associated with NCLs, see Table A, **Gene**.

PPT1

Gene structure. The gene comprises nine exons spanning 25 kb.

Pathogenic variants. More than 60 pathogenic variants of *PPT1* are known. The common pathogenic variants are p.Arg122Trp and p.Arg151Ter [Das et al 1998]; the others are uncommon or private variants.

Table 6. *PPT1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.364A>T	p.Arg122Trp	NM_000310.2 NP_000301.1
c.451C>T	p.Arg151Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. PPT-1 is a globular enzyme consisting of six parallel β strands alternating with α helices organized in a structure known as the α/β hydrolast fold typical of lipases. A large insertion between β6 and β7 (amino acid residues 140-223) forms a second domain that forms most of the fatty acid-binding site. Catalytic active site residues are: Ser115, Asp233, and His289. PPT-1 is a housekeeping enzyme present in the lysosomes of many tissues. It removes long-chain fatty acids, usually palmitate, from cystine residues.

Based on the results of crystallographic and molecular modeling studies of recombinant bovine PPT-1 enzyme, a mechanism has been hypothesized to explain the milder INCL phenotype in individuals with *PPT1* pathogenic variants who retain low-level thioesterase activity [Bellizzi et al 2000].

Abnormal gene product. Pathogenic variants affect PPT-1 in different ways. For some the protein is truncated, lacking its catalytic site; for others critical residues, such as within the catalytic site, are absent or altered.

TPP1

Gene structure. *TPP1* comprises 13 exons.

Pathogenic variants. More than 90 pathogenic variants of *TPP1* are known. The common pathogenic variants are p.Arg208Ter and c.509-1G>C [Zhong et al 1998, Sleat et al 1999]; the others are uncommon or private variants.

Table 7. *TPP1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.622C>T	p.Arg208Ter	NM_000391.3 NP_000382.3
c.509-1G>C (IVS5-1G>C)	--	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. TPP-1 comprises 365 amino acids. It is a lysosomal serine-carboxyl peptidase that sequentially removes N-terminal tripeptides from small peptides, including several peptide hormones.

Abnormal gene product. Pathogenic variants affect TPP-1 in different ways. For some the protein is truncated, lacking its catalytic site; for others critical residues, such as within the catalytic site, are absent or altered.

CLN3

Gene structure. The gene comprises 15 exons.

Pathogenic variants. More than 50 pathogenic variants are presently known. The common pathogenic variant is c.461-280_677+382del [Munroe et al 1997]; the others are uncommon or private variants. The c.461-280_677+382del variant deletes 217 bp of coding sequence, but the breakpoints are in intronic regions and the total deletion is approximately 1 kb and includes exons 7 and 8. The genomic DNA designation is NG_008654.1:g.10373_11338del.

Table 8. *CLN3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.461-280_677+382del (c.461_677del)	p.Gly154AlafsTer29	NM_001042432.1 NP_001035897.1
c.88G>A	p.Glu295Lys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. The protein comprises 438 amino acids; its function is unknown. *CLN3* is most likely to be present in the lysosomal/endosomal membrane, and may also be in the Golgi complex and on the plasma membrane. In addition, *CLN3* undergoes post-translational modification.

Abnormal gene product. Although the function of *CLN3* remains elusive, it is apparent that genetic alterations in *CLN3* may have a direct effect on lysosomal function. The most common pathogenic variant, the 1-kb deletion, does not completely abolish CLN3 function [Kitzmüller et al 2008].

DNAJC5

Gene structure. The transcript has five exons [NM_025219.2].

Pathogenic variants. Two pathogenic variants have been described [Nosková et al 2011].

Normal gene product. The protein, DnaJ homolog subfamily C member 5, functions in many cellular processes by regulating the ATPase activity of 70-kd heat shock proteins [provided by RefSeq].

Abnormal gene product. Two variants that cause disease when present on a single allele of *DNAJC5* have been identified; the mechanism is unknown.

CLN5

Gene structure. The gene comprises four exons.

Pathogenic variants. More than 30 pathogenic variants are known. The first affected individuals were in Finland; many cases have now been reported elsewhere. The pathogenic variant p.Tyr392Ter is observed in 94% of individuals of Finnish descent who have CLN5; the pathogenic variant p.Trp75Ter also segregates in affected individuals of Finnish descent. Other pathogenic variants are less common.

Table 9. *CLN5* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.225G>A	p.Trp75Ter	NM_006493.1 NP_006484.1
c.1175_1176delAT	p.Tyr392Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The normal protein comprises 407 amino acids.

Abnormal gene product. *CLN5* is a lysosomal transmembrane or soluble protein of unknown function.

CLN6

Gene structure. The gene comprises seven exons.

Pathogenic variants. More than 60 pathogenic variants are known, including missense and nonsense variants, small deletions or insertions, and splice site variants. Affected individuals have been identified in many countries. The pathogenic variant p.Glu72Ter is common in persons from Costa Rica. The 1-bp insertion c.316dupC is associated with families from Pakistan; p.Ile154del may be common in Portugal. See Table 10.

Table 10. *CLN6* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.214G>T	p.Glu72Ter	NM_017882.1 NP_060352.1
c.316dupC (c.316insC)	p.Arg106ProfsTer6	
c.460_462delATC	p.Ile154del	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. This transmembrane protein of unknown function resides in the endoplasmic reticulum (ER) [Mole et al 2004].

Abnormal gene product. Heine et al [2004] discuss the defective endoplasmic reticulum resulting from *CLN6* pathogenic variants.

MFSD8

Gene structure. The gene comprises 13 exons.

Pathogenic variants. More than 30 pathogenic variants are known. Variants in *MFSD8* were originally identified in persons of Turkish origin; cases from many countries have since been described. The most common pathogenic variant is p.Thr294Lys, which is associated with Roma Gypsies originating from the Czech Republic. Another common pathogenic variant is c.754+2T>A. See Table 11.

Table 11. *MFSD8* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change
c.881C>A [1]	p.Thr294Lys
c.754+2T>A [2]	(predicted altered splicing)

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Kousi et al [2009]
2. Siintola et al [2007]

Normal gene product. MFSD8 is a member of the major facilitator superdomain family of transporter proteins.

Abnormal gene product. Unknown

CLN8

Gene structure. The gene comprises three exons.

Pathogenic variants. More than 20 pathogenic variants are known. Many variants have been reported in persons from several countries, including Turkey and Italy.

One group of individuals of Finnish origin, who are homozygous for the missense variant p.Arg24Gly, have the allele-specific disease Northern epilepsy/EPMR disease [Ranta et al 2001]. Other pathogenic variants in *CLN8* give rise to the vLINCL phenotype.

Table 12. *CLN8* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.70C>G	p.Arg24Gly	NM_018941.3 NP_061764.2

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GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. This protein of 286 amino acids is localized to the ER and ER Golgi intermediate compartment.

Abnormal gene product. Unknown

CTSD (previously *CLN10*)

Gene structure. The transcript NM_001909.4 comprises nine exons.

Pathogenic variants. Seven pathogenic variants are known. None is common (see Table A, **Locus Specific**).

Normal gene product. NP_001900.1 has 412 amino acid residues that encode cathepsin D light chain, a lysosomal aspartate protease**.**

Abnormal gene product. Unknown

GRN

Gene structure. Transcript NM_002087.2 has 13 exons.

Pathogenic variants. Two NCL-causing variants have been described [Smith et al 2012] (see Table A, **Locus Specific**).

Normal gene product. Granulins are a family of secreted, glycosylated peptides that are cleaved from a single precursor protein with 7.5 repeats of a highly conserved 12-cysteine granulin/epithelin motif. The 88-kd precursor protein, progranulin, is also called proepithelin [extracted from RefSeq]. Transcript NM_002087.2 encodes a mature peptide of 576 amino acids, NP_002078.1.

Abnormal gene product. A variant on one disease allele only causes late-onset frontotemporal lobe degeneration with TDP-43 inclusions. Variants on both disease alleles cause childhood-onset NCL. The mechanism is unknown.

ATP13A2

Gene structure. The longest transcript variant NM_022089.2 has 29 exons and encodes the longest protein isoform. Other transcript variants have been found.

Pathogenic variants. One pathogenic variant that results in NCL has been described [Bras et al 2012].

Normal gene product. The protein product ATP13A2 is a P-type ATPase. The longest isoform NP_071372.1 has 1180 amino acids.

Abnormal gene product. Unknown

CTSF

Gene structure. The transcript NM_003793.3 comprises 13 exons.

Pathogenic variants. Five pathogenic variants have been described [Smith et al 2013].

Normal gene product. The protein product, cathepsin F, has 484 amino acid residues. Cathepsins are papain family cysteine proteinases that represent a major component of the lysosomal proteolytic system [extracted from RefSeq].

Abnormal gene product. Unknown, but enzyme activity is presumably impaired.

KCTD7

Gene structure. NM_153033.4 is the longest transcript variant and comprises four exons.

Pathogenic variants. One NCL-causing variant has been described [Staropoli et al 2012].

Normal gene product. The gene product, BTB/POZ domain-containing protein KCTD7, is a potassium channel tetramerization domain-containing protein 7.

Abnormal gene product. Unknown, but different pathogenic variants cause different diseases.

References

Literature Cited

Aberg L, Kirveskari E, Santavuori P. Lamotrigine therapy in juvenile neuronal ceroid lipofuscinosis. Epilepsia. 1999;40:796–9. PubMed PMID: 10368082.

Aberg LE, Backman M, Kirveskari E, Santavuori P. Epilepsy and antiepileptic drug therapy in juvenile neuronal ceroid lipofuscinosis. Epilepsia. 2000;41:1296–302. PubMed PMID: 11051125.

Arsov T, Smith KR, Damiano J, Franceschetti S, Canafoglia L, Bromhead CJ, Andermann E, Vears DF, Cossette P, Rajagopalan S, McDougall A, Sofia V, Farrell M, Aguglia U, Zini A, Meletti S, Mullen S, Morbin M, Mullen M, Andermann F, Mole S, Bahlo M, Berkovic SF. Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in CLN6. Am J Hum Genet. 2011;88:566–73. PubMed PMID: 21549341.

Bäckman ML, Santavuori PR, Aberg LE, Aronen ET. Psychiatric symptoms of children and adolescents with juvenile neuronal ceroid lipofuscinosis. J Intellect Disabil Res. 2005;49:25–32. PubMed PMID: 15634309.

Bellizzi JJ 3rd, Widom J, Kemp C, Lu JY, Das AK, Hofmann SL, Clardy J. The crystal structure of palmitoyl protein thioesterase 1 and the molecular basis of infantile neuronal ceroid lipofuscinosis. Proc Natl Acad Sci U S A. 2000;97:4573–8. PubMed PMID: 10781062.

Burneo JG, Arnold T, Palmer CA, Kuzniecky RI, Oh SJ, Faught E. Adult-onset neuronal ceroid lipofuscinosis (Kufs disease) with autosomal dominant inheritance in Alabama. Epilepsia. 2003;44:841–6. PubMed PMID: 12790899.

Bras J, Verloes A, Schneider SA, Mole SE, Guerreiro RJ. Mutation of the parkinsonism gene ATP13A2 causes neuronal ceroid-lipofuscinosis. Hum Mol Genet. 2012;21:2646–50. PubMed PMID: 22388936.

Crystal RG, Sondhi D, Hackett NR, Kaminsky SM, Worgall S, Stieg P, Souweidane M, Hosain S, Heier L, Ballon D, Dinner M, Wisniewski K, Kaplitt M, Greenwald BM, Howell JD, Strybing K, Dyke J, Voss H. Clinical protocol. Administration of a replication-deficient adeno-associated virus gene transfer vector expressing the human CLN2 cDNA to the brain of children with late infantile neuronal ceroid lipofuscinosis. Hum Gene Ther. 2004;15:1131–54. PubMed PMID: 15610613.

Das AK, Becerra CH, Yi W, Lu JY, Siakotos AN, Wisniewski KE, Hofmann SL. Molecular genetics of palmitoyl-protein thioesterase deficiency in the U.S. J Clin Invest. 1998;102:361–70. PubMed PMID: 9664077.

Gao H, Boustany RM, Espinola JA, Cotman SL, Srinidhi L, Antonellis KA, Gillis T, Qin X, Liu S, Donahue LR, Bronson RT, Faust JR, Stout D, Haines JL, Lerner TJ, MacDonald ME. Mutations in a novel CLN6-encoded transmembrane protein cause variant neuronal ceroid lipofuscinosis in man and mouse. Am J Hum Genet. 2002;70:324–35. PubMed PMID: 11791207.

Hartikainen JM, Ju W, Wisniewski KE, Moroziewicz DN, Kaczmarski AL, McLendon L, Zhong D, Suarez CT, Brown WT, Zhong N. Late infantile neuronal ceroid lipofuscinosis is due to splicing mutations in the CLN2 gene. Mol Genet Metab. 1999;67:162–8. PubMed PMID: 10356316.

Heine C, Koch B, Storch S, Kohlschutter A, Palmer DN, Braulke T. Defective endoplasmic reticulum-resident membrane protein CLN6 affects lysosomal degradation of endocytosed arylsulfatase A. J Biol Chem. 2004;279:22347–52. PubMed PMID: 15010453.

Hofmann SL, Das AK, Yi W, Lu JY, Wisniewski KE. Genotype-phenotype correlations in neuronal ceroid lipofuscinosis due to palmitoyl-protein thioesterase deficiency. Mol Genet Metab. 1999;66:234–9. PubMed PMID: 10191107.

Junaid MA, Sklower Brooks S, Wisniewski KE, Pullarkat RK. A novel assay for lysosomal pepstatin-insensitive proteinase and its application for the diagnosis of late-infantile neuronal ceroid lipofuscinosis. Clin Chim Acta. 1999;281:169–76. PubMed PMID: 10217638.

Kitzmüller C, Haines RL, Codlin S, Cutler DF, Mole SE. A function retained by the common mutant CLN3 protein is responsible for the late onset of juvenile neuronal ceroid lipofuscinosis. Hum Mol Genet. 2008;17:303–12. PubMed PMID: 17947292.

Kousi M, Siintola E, Dvorakova L, Vlaskova H, Turnbull J, Topcu M, Yuksel D, Gokben S, Minassian BA, Elleder M, Mole SE, Lehesjoki AE. Mutations in CLN7/MFSD8 are a common cause of variant late-infantile neuronal ceroid lipofuscinosis. Brain. 2009;132:810–9. PubMed PMID: 19201763.

Lauronen L, Munroe PB, Järvelä I, Autti T, Mitchison HM, O'Rawe AM, Gardiner RM, Mole SE, Puranen J, Häkkinen AM, Kirveskari E, Santavuori P. Delayed classic and protracted phenotypes of compound heterozygous juvenile neuronal ceroid lipofuscinosis. Neurology. 1999;52:360–5. PubMed PMID: 9932957.

Leman AR, Pearce DA, Rothberg PG. Gene symbol: CLN3. Disease: Juvenile neuronal ceroid lipofuscinosis (Batten disease). Hum Genet. 2005;116:544. PubMed PMID: 15991331.

Mao Q, Xia H, Davidson BL. Intracellular trafficking of CLN3, the protein underlying the childhood neurodegenerative disease, Batten disease. FEBS Lett. 2003;555:351–7. PubMed PMID: 14644441.

Mole SE, Michaux G, Codlin S, Wheeler RB, Sharp JD, Cutler DF. CLN6, which is associated with a lysosomal storage disease, is an endoplasmic reticulum protein. Exp Cell Res. 2004;298:399–406. PubMed PMID: 15265688.

Mole SE, Williams RE, Goebel HH. *The Neuronal Ceroid Lipofuscinoses (Batten Disease).* 2 ed. Oxford, UK: Oxford University Press; 2011.

Munroe PB, Mitchison HM, O'Rawe AM, Anderson JW, Boustany RM, Lerner TJ, Taschner PE, de Vos N, Breuning MH, Gardiner RM, Mole SE. Spectrum of mutations in the Batten disease gene, CLN3. Am J Hum Genet. 1997;61:310–6. PubMed PMID: 9311735.

Nijssen PC, Ceuterick C, van Diggelen OP, Elleder M, Martin JJ, Teepen JL, Tyynela J, Roos RA. Autosomal dominant adult neuronal ceroid lipofuscinosis: a novel form of NCL with granular osmiophilic deposits without palmitoyl protein thioesterase 1 deficiency. Brain Pathol. 2003;13:574–81. PubMed PMID: 14655761.

Nosková L, Stránecký V, Hartmannová H, Přistoupilová A, Barešová V, Ivánek R, Hůlková H, Jahnová H, van der Zee J, Staropoli JF, Sims KB, Tyynelä J, Van Broeckhoven C, Nijssen PC, Mole SE, Elleder M, Kmoch S. Mutations in DNAJC5, encoding cysteine-string protein alpha, cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis. Am J Hum Genet. 2011;89:241–52. PubMed PMID: 21820099.

Ostergaard JR, Rasmussen TB, Mølgaard H. Cardiac involvement in juvenile neuronal ceroid lipofuscinosis (Batten disease). Neurology. 2011;76:1245–51. PubMed PMID: 21464428.

Ramadan H, Al-Din AS, Ismail A, Balen F, Varma A, Twomey A, Watts R, Jackson M, Anderson G, Green E, Mole SE. Adult neuronal ceroid lipofuscinosis caused by deficiency in palmitoyl protein thioesterase 1. Neurology. 2007;68:387–8. PubMed PMID: 17261688.

Ranta S, Savukoski M, Santavuori P, Haltia M. Studies of homogenous populations: CLN5 and CLN8. In: Wisniewski KE, Zhong N, eds. *Batten Disease: Diagnosis, Treatment, and Research* (*Advances in Genetics*, vol 45). San Diego, CA: Academic Press; 2001:123-40

Ranta S, Topcu M, Tegelberg S, Tan H, Ustubutun A, Saatci I, Dufke A, Enders H, Pohl K, Alembik Y, Mitchell WA, Mole SE, Lehesjoki AE. Variant late infantile neuronal ceroid lipofuscinosis in a subset of Turkish patients is allelic to Northern epilepsy. Hum Mutat. 2004;23:300–5. PubMed PMID: 15024724.

Riikonen R, Vanhanen SL, Tyynela J, Santavuori P, Turpeinen U. CSF insulin-like growth factor-1 in infantile neuronal ceroid lipofuscinosis. Neurology. 2000;54:1828–32. PubMed PMID: 10802792.

Savukoski M, Klockars T, Holmberg V, Santavuori P, Lander ES, Peltonen L. CLN5, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late infantile neuronal ceroid lipofuscinosis. Nat Genet. 1998;19:286–8. PubMed PMID: 9662406.

Schulz A, Dhar S, Rylova S, Dbaibo G, Alroy J, Hagel C, Artacho I, Kohlschütter A, Lin S, Boustany RM. Impaired cell adhesion and apoptosis in a novel CLN9 Batten disease variant. Ann Neurol. 2004;56:342–50. PubMed PMID: 15349861.

Schulz A, Kohlschütter A, Mink J, Simonati A, Williams R. NCL diseases - clinical perspectives. Biochim Biophys Acta. 2013;1832:1801–6. PubMed PMID: 23602993.

Sharp JD, Wheeler RB, Parker KA, Gardiner RM, Williams RE, Mole SE. Spectrum of CLN6 mutations in variant late infantile neuronal ceroid lipofuscinosis. Hum Mutat. 2003;22:35–42. PubMed PMID: 12815591.

Siintola E, Topcu M, Aula N, Lohi H, Minassian BA, Paterson AD, Liu XQ, Wilson C, Lahtinen U, Anttonen AK, Lehesjoki AE. The novel neuronal ceroid lipofuscinosis gene MFSD8 encodes a putative lysosomal transporter. Am J Hum Genet. 2007;81:136–46. PubMed PMID: 17564970.

Sleat DE, Gin RM, Sohar I, Wisniewski K, Sklower-Brooks S, Pullarkat RK, Palmer DN, Lerner TJ, Boustany RM, Uldall P, Siakotos AN, Donnelly RJ, Lobel P. Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. Am J Hum Genet. 1999;64:1511–23. PubMed PMID: 10330339.

Smith KR, Damiano J, Franceschetti S, Carpenter S, Canafoglia L, Morbin M, Rossi G, Pareyson D, Mole SE, Staropoli JF, Sims KB, Lewis J, Lin WL, Dickson DW, Dahl HH, Bahlo M, Berkovic SF. Strikingly different clinicopathological phenotypes determined by progranulin mutation dosage. Am J Hum Genet. 2012;90:1102–7. PubMed PMID: 22608501.

Smith KR, Dahl HH, Canafoglia L, Andermann E, Damiano J, Morbin M, Bruni AC, Giaccone G, Cossette P, Saftig P, Grötzinger 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. Cathepsin F mutations cause Type B Kufs disease, an adult-onset neuronal ceroid lipofuscinosis. Hum Mol Genet. 2013;22:1417–23. PubMed PMID: 23297359.

Staropoli JF, Karaa A, Lim ET, Kirby A, Elbalalesy N, Romansky SG, Leydiker KB, Coppel SH, Barone R, Xin W, MacDonald ME, Abdenur JE, Daly MJ, Sims KB, Cotman SL. A homozygous mutation in KCTD7 links neuronal ceroid lipofuscinosis to the ubiquitin-proteasome system. Am J Hum Genet. 2012; 2012;91:202–8. PubMed PMID: 22748208.

Teixeira CA, Espinola J, Huo L, Kohlschutter J, Persaud Sawin DA, Minassian B, Bessa CJ, Guimaraes A, Stephan DA, Sa Miranda MC, MacDonald ME, Ribeiro MG, Boustany RM. Novel mutations in the CLN6 gene causing a variant late infantile neuronal ceroid lipofuscinosis. Hum Mutat. 2003;21:502–8. PubMed PMID: 12673792.

van Diggelen OP, Thobois S, Tilikete C, Zabot MT, Keulemans JL, van Bunderen PA, Taschner PE, Losekoot M, Voznyi YV. Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: first adult-onset patients of a childhood disease. Ann Neurol. 2001;50:269–72. PubMed PMID: 11506414.

Verity C, Winstone AM, Stellitano L, Will R, Nicoll A. The epidemiology of progressive intellectual and neurological deterioration in childhood. Arch Dis Child. 2010;95:361–4. PubMed PMID: 19948513.

Voznyi YV, Keulemans JL, Mancini GM, Catsman-Berrevoets CE, Young E, Winchester B, Kleijer WJ, van Diggelen OP. A new simple enzyme assay for pre- and postnatal diagnosis of infantile neuronal ceroid lipofuscinosis (INCL) and its variants. J Med Genet. 1999;36:471–4. PubMed PMID: 10874636.

Weleber RG. The dystrophic retina in multisystem disorders: the electroretinogram in neuronal ceroid lipofuscinoses. Eye. 1998;12:580–90. PubMed PMID: 9775220.

Williams RE, Mole SE. New nomenclature and classification scheme for the neuronal ceroid lipofuscinoses. Neurology. 2012;79:183–91. PubMed PMID: 22778232.

Wiśniewski KE, Kaczmarski A, Kida E, Connell F, Kaczmarski W, Michalewski MP, Moroziewicz DN, Zhong N. Reevaluation of neuronal ceroid lipofuscinoses: atypical juvenile onset may be the result of CLN2 mutations. Mol Genet Metab. 1999;66:248–52. PubMed PMID: 10191110.

Wiśniewski KE, Zhong N, Kaczmarski W, Kaczmarski A, Kida E, Brown WT, Schwarz KO, Lazzarini AM, Rubin AJ, Stenroos ES, Johnson WG, Wisniewski TM. Compound heterozygous genotype is associated with protracted juvenile neuronal ceroid lipofuscinosis. Ann Neurol. 1998a;43:106–10. PubMed PMID: 9450775.

Wiśniewski KE, Zhong N, Kaczmarski W, Kaczmarski A, Sklower-Brooks S, Brown WT. Studies of atypical JNCL suggest overlapping with other NCL forms. Pediatr Neurol. 1998b;18:36–40. PubMed PMID: 9492089.

Wiśniewski KE, Zhong N, Philippart M. Pheno/genotypic correlations of neuronal ceroid lipofuscinoses. Neurology. 2001;57:576–81. PubMed PMID: 11548735.

Zhong N, Moroziewicz DN, Ju W, Jurkiewicz A, Johnston L, Wisniewski KE, Brown WT. Heterogeneity of late-infantile neuronal ceroid lipofuscinosis. Genet Med. 2000a;2:312–8. PubMed PMID: 11339651.

Zhong N, Wisniewski KE, Hartikainen J, Ju W, Moroziewicz DN, McLendon L, Sklower Brooks SS, Brown WT. Two common mutations in the CLN2 gene underlie late infantile neuronal ceroid lipofuscinosis. Clin Genet. 1998;54:234–8. PubMed PMID: 9788728.

Zhong NA, Wisniewski KE, Ju W, Moroziewicz DN, Jurkiewicz A, McLendon L, Jenkins EC, Brown WT. Molecular diagnosis of and carrier screening for the neuronal ceroid lipofuscinoses. Genet Test. 2000b;4:243–8. PubMed PMID: 11142754.

Zupanc ML, Legros B. Progressive myoclonic epilepsy. Cerebellum. 2004;3:156–71. PubMed PMID: 15543806.

Chapter Notes

Author Notes

The original author, Dr Wiśniewski, was a nationally and internationally known pediatric neurologist and neuropathologist/neurobiologist. She was the author or co-author of more than 300 publications and numerous books and book chapters in the field of progressive neurogenetic diseases and intellectual and developmental disabilities. Dr Wiśniewski died of complications of cancer on May 30, 2008.

Current author Sara Mole, PhD is a research scientist with more than 20 years' experience in the neuronal ceroid lipofuscinoses. She curates the NCL Mutation Database, part of the NCL Resource website, and is an author of many scientific articles, reviews, and book chapters, as well as editor of a book on Batten disease.

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Revision History

- 11 April 2019 (ma) Chapter retired: Chapter does not reflect current use of genetic testing.
- 1 August 2013 (me) Comprehensive update posted live
- 2 March 2010 (me) Comprehensive update posted live
- 17 May 2006 (me) Comprehensive update posted live

- 15 August 2005 (bp) Revision: sequence analysis for CLN5 and CLN8 clinically available
- 19 November 2004 (bp) Revision: *CLN5* and *CLN8* sequence analysis
- 27 January 2004 (me) Comprehensive update posted live
- 12 June 2003 (kw) Revision: testing
- 10 October 2001 (me) Review posted live
- 20 February 2001 (kw) Original submission

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