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Genetics of the Neuronal Ceroid Lipofuscinoses (Batten disease)

Sara E Mole[1,2] and **Susan L. Cotman**[3]

[1]MRC Laboratory for Molecular Cell Biology, University College London, Gower Street, London WC1E 6BT, UK

[2]UCL Institute of Child Health, Department of Genetics, Evolution and Environment, University College London, London WC1E 6BT, UK

[3]Center for Human Genetic Research, Department of Neurology, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114, U.S.A

Abstract

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited neurodegenerative disorders that affect children and adults, and are grouped together by similar clinical features and the accumulation of autofluorescent storage material. More than a dozen genes containing over 430 mutations underlying human NCLs have been identified. These genes encode lysosomal enzymes (CLN1, CLN2, CLN10, CLN13), a soluble lysosomal protein (CLN5), a protein in the secretory pathway (CLN11), two cytoplasmic proteins that also peripherally associate with membranes (CLN4, CLN14), and many transmembrane proteins with different subcellular locations (CLN3, CLN6, CLN7, CLN8, CLN12). For most NCLs, the function of the causative gene has not been fully defined. Most of the mutations in these genes are associated with a typical disease phenotype, but some result in variable disease onset, severity and progression, including distinct clinical phenotypes. There remain disease subgroups with unknown molecular genetic backgrounds. This article is part of a Special Issue entitled: The Neuronal Ceroid Lipofuscinoses or Batten Disease.

Keywords

Batten; CLN; neuronal ceroid lipofuscinosis; NCL; genetics; mutation

Corresponding author: Sara Mole, MRC Laboratory for Molecular Cell Biology, University College London, Gower Street, London WC1E 6BT, UK. s.mole@ucl.ac.uk. Tel +44 207 679 7257, Fax +44 207 679 7805.

Database Linking

Please link to

NCL Resource: http://www.ucl.ac.uk/ncl/index.shtml

NCL Mutation Database: http://www.ucl.ac.uk/ncl/mutation.shtml

COSMIC: http://www.sanger.ac.uk/genetics/CGP/cosmic/)

Exome Aggregation Consortium (ExAC): http://exac.broadinstitute.org

The neuronal ceroid lipofuscinoses share common clinical features that include epileptic seizures, progressive psychomotor decline, visual failure, and premature death. NCL disease usually begins in childhood, and most types are inherited in an autosomal recessive manner. However, there are several types with onset in early to late adulthood, including one type with autosomal dominant inheritance. Mutations in more than a dozen genes have been described in families diagnosed with NCL disease (Table 1). Those genes that cause the most prevalent and typical NCL disease with onset in childhood have been identified. There remain families diagnosed with NCL of all ages of onset in which the underlying genetic cause has not been described. Thus far, these cases do not appear to be caused by mutations in other genes that cause NCL-like disease in animals.

The aim of this review is to briefly summarise the genetic basis of NCL and any correlations with disease phenotype. Details on mutations can be found in the NCL mutation database (http://www.ucl.ac.uk/ncl).

NCL disease was first divided into four broad ages of onset in the late 1960s: infantile, late infantile, juvenile and adult, due to initial simple supposition that there are four genes responsible for NCL disease, *CLN1*, *CLN2*, *CLN3* and *CLN4*, respectively. The first genes to be identified were in the most common subtypes (*CLN1*, *CLN2*, *CLN3*). However, it was many years, with several further genes identified in less common forms of NCL, before a gene encoding the rare dominant adult type was found (*CLN4*). A variety of experimental approaches, largely reflective of the available technology at the time of identification, were used to identify genes causing NCL (Table 1). The first genes were discovered in 1995 following classic and time-consuming genetic linkage approaches using large numbers of similarly affected families followed by positional cloning of the genes (*CLN1/PPT1* and *CLN3*). In contrast, a biochemical approach that detected a missing mannose-6-phosphate tagged lysosomal enzyme in a patient allowed the identification of *CLN2/TPP1*. The next wave of gene identification required fewer families to provide sufficient power for genetic linkage analysis, due to the completion of the sequence of the human genome that provided more informative sequence variants (*CLN5*, *CLN6*, *CLN7/MFSD8*, *CLN8*). Several of these genes were identified by narrowing the candidate gene region by recognition of the stretches of homozygosity in consanguineous families. Recent improvements in sequencing technology that permits massively parallel sequencing of the whole exome in a relatively short space of time has allowed identification of the disease gene even in single families (*CLN4/DNAJC5*, *CLN11/GRN*, *CLN12/ATP13A2*, *CLN13/CTSF*, *CLN14/KCTD7*).

All NCL genes lie on autosomes and in most cases disease is inherited in a recessive manner, where deleterious mutations are present in both disease gene alleles. There are two notable exceptions: (1) adult onset NCL caused by mutations in *CLN4/DNAJC5* is dominantly inherited in all families described [1]; (2) There is one published report of uniparental disomy in the NCLs, in which a patient with complete isodisomy of chromosome 8, leading to homozygosity of a maternally-inherited deletion in *CLN8* is described [2].

The majority of NCL genes encode proteins that reside in the secretory and/or endo/lysosomal pathways. In most cases, these are lysosomal proteins, which include enzymes

and a soluble protein (encoded by *CLN1/PPT1*, *CLN2/TPP1*, *CLN5*, *CLN10/CTSD*, *CLN13/CTSF*) and transmembrane proteins (encoded by *CLN3*, *CLN6*, *CLN7/MFSD8*, *CLN12/ATP13A2*). However, the transmembrane proteins CLN6 and CLN8 both localize to the endoplasmic reticulum (ER), and progranulin, encoded by *CLN11*/*GRN*, is demonstrated to reside in compartments in the secretory pathway [3]. Two other NCL proteins, encoded by *CLN4/DNAJC5* and *CLN14/KCTD7*, are both cytoplasmic and peripherally associated with cellular membranes. The *in vivo* substrates for the soluble lysosomal enzymes are incompletely defined, and knowledge regarding the primary functions of the membrane proteins in these compartments largely remains unresolved.

For the enzymatic deficiencies, enzyme replacement and gene therapy are promising approaches that are actively undergoing clinical development [4]. However, the unresolved functions for the other NCL proteins, which are less compatible with gene/protein replacement approaches, remains problematic for targeted therapy development. It is unclear which cellular defects due to their loss of function are primary versus secondary, and which of these defects play a central role in the cellular dysfunction and death that ensues. Despite these gaps in understanding of NCL protein function, there is wide evidence to indicate that cellular processes involving lipid and protein trafficking in the endocytic pathway and the regulation of endosomal and lysosomal transport are points of convergence for a number of the NCL protein deficiencies. A detailed overview of the current understanding of function for each of the NCL-encoded proteins can be found in this special issue [5].

For most NCL genes there is a typical disease phenotype associated with complete loss of function. However, for many there are also phenotypes recognised as NCL that are more protracted or have a later age of onset (Table 2). These arise from mutations that have ‘milder’ effects on gene function, and these phenotypes can vary quite considerably. For example, classic CLN6 disease begins in early childhood, but disease onset can be delayed until adulthood, with no associated visual failure [6]. There is also clinically similar NCL disease arising from mutations in more than one gene (e.g. late infantile variant NCL can be caused by mutations in *CLN5*, *CLN6*, *CLN7*, or *CLN8*). This led to the development of a new classification system that is gene-based and takes into account these marked phenotypic consequences [7].

There are an increasing number of examples of different mutations in a single gene giving rise to quite different diseases (Table 2): (1) A recessive missense mutation in *CLN8* [8] causes progressive epilepsy with mental retardation (EPMR). This disease is an intellectual developmental disorder that presents with seizures in the juvenile age range that cease at adulthood, and was the first genetic disease to be recognised for *CLN8*. Mutations that cause a more typical NCL were described later; (2) A particular missense mutation in CLN2/TPP1 is associated with spinocerebellar ataxia SCAR7, a slowly progressing but not life-limiting disease with no ophthalmologic abnormalities or epilepsy, and absence of typical storage [9]; A homozygous recessive mutation in *GRN* that is associated with rectilinear profiles, as found in progranulin-deficient mice [10], leads to CLN11 disease, whereas heterozygous mutations are a major cause of frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), the second most common type of early-onset dementia. In this NCL family, it seems that carriers of this mutation are at risk of developing dementia with increasing age,

which had been masked by the early death of many older members on both sides of the family. The age-at-onset and neuropathology of FTLD-TDP and NCL are markedly different and exemplify genetic links that have been emerging between rare diseases and common neurological disorders, such as Niemann-Pick C disease with Alzheimer's disease [11] and type 1 Gaucher disease with Parkinson's disease [12]; (3) Evidence suggests that the most common and very widespread mutation in *CLN3*, a 1-kb deletion, does not completely abolish CLN3 function, suggesting that disease caused by complete loss of function has not yet been recognized or may be lethal [13];. Other recently described distinct phenotypes associated with *CLN3* mutations include retinitis pigmentosa without other clinical symptoms, even in mid-late adulthood [14] and a distinct disease described as autophagic myopathy associated with heart failure [15], considerably extending the phenotype of *CLN3*-associated disease; (4) There are also reports of other families with mutations in NCL genes that have predominantly visual problems [16]; (5) The only autosomal dominant type of NCL is CLN4 disease. Disease caused by complete loss of CLN4 function is not known, although animal models would predict very severe and early onset disease; (6) Mutations in *CLN14/KCTD7* have now been reported to cause three different diseases including NCL-like CLN14 disease [17–20]; (7). One family has been diagnosed with CLN12 disease, an atypical NCL [21], whereas all other mutations in *ATP13A2* cause Kufor-Rakeb syndrome; (8) One mutation in *SGSH* was described in a case diagnosed with adult onset NCL. Mutations in this gene usually underlie late infantile onset disease mucopolysaccharidosis type IIIA (MPSIIIA) [22].

Mutations in NCL genes range from those that are described in one or only a few families, to those that are more common in certain populations due to local founder effects. Several NCL genes have widespread distribution across several continents due to ancient founder effects (Table 2). The common mutation causing juvenile CLN3 disease is the best example of this, though it is unclear whether this global spreading provided a genetic advantage in the past. Diagnostic testing can be appropriately targeted to these common mutations.

There are reports of patients carrying changes in more than one NCL gene. One that was later found to be compound heterozygous for mutations in *CLN5* also carries a single mutation in the *CLCN6* gene. Another family has been described in which a single mutation in *CLCN6* is the only reported variation. It is assumed that a second heterozygous mutation is present but not identified, as the *CLCN6* carrier parents in both families were not affected, and a mouse model lacking *CLCN6* clearly has an NCL-like disease. Some patients carry mutations in more than one gene that underlie variant late infantile NCL (e.g. the mutation database lists changes in *CLN5* that have been found alongside those in *CLN6* or *CLN7* or *CLN8*). These may be examples of a mutation or specific allele of one gene enhancing or ameliorating the NCL disease phenotype.

There are also several reports that implicate NCL genes in a wider biology of disease: (1) Combinations of mutations may cause a markedly modified disease course, such as a patient with disease that presented shortly after birth who was found to carry heterozygous mutations in CLN5, together with a mutation in POLG1 that acts to maintain mitochondrial DNA integrity [23]. (2) Increased expression of CLN8 may act as a modifier of Gaucher disease [24]. (3) Somatic mutations in all known NCL genes are acquired in human cancer

cells (COSMIC) and may confer a growth advantage (*CLN1/PPT1*, *CLN2/TPP1*, *CLN3*, *CLN4/DNAJC5*, *CLN5*, *CLN6*, *CLN7/MFSD8*, *CLN8*, *CLN10/CTSD*, *CLN11/GRN*, *CLN12/ATP13A2*, *CLN13/CTSF*, *CLN14/*KCTD7, as well as *SGSH* and *CLCN6*) (http://www.sanger.ac.uk/genetics/CGP/cosmic/) [25]. Further correlations may be revealed with the increasing number of sequence variations that are being described by large-scale genome sequencing projects (e.g. Exome Aggregation Consortium (ExAC): http://exac.broadinstitute.org).

It is likely that some patients diagnosed with NCL may really have atypical forms of other diseases. However, a distinction between disease phenotypes may not be as clear cut as originally thought. Advances in DNA sequencing technology are likely to lead to the identification of the disease gene causing any atypical disease. It may be timely to review the criteria that define the NCL family of diseases. This could be considered by a recognised group of experts at the next international congress to be held in 2016, following the working pattern already established that discussed, devised and then recommended a new gene-based disease nomenclature for the NCLs.

It can be predicted from observations in mouse or other animal models that mutations in some genes cause disease that is similar to NCL even though the disease described in humans so far is not similar. For example, *CLCN7* underlies the severe autosomal recessive disease infantile malignant osteopetrosis, and when the osteopetrosis is treated with bone marrow transplantation, patients go on to develop blindness and CNS degeneration, suggesting that specific mutations or alleles in this gene may cause NCL-like disease. Intriguingly, recent evidence in cattle indicates that mutations in *CLCN7* also underlie severe gingival hamartomas and osteopetrosis, with evidence suggesting NCL-like lysosomal storage is present in these animals [26].

The NCL Mutation Database (http://www.ucl.ac.uk/ncl) lists all mutations and sequence variations in NCL genes. 446 NCL disease-causing mutations are currently listed (Table 3). This Mutation Database includes the genetic basis of NCL disease in all patients and families (>1270) reported in clinical or scientific publications to allow better correlation between gene changes and disease phenotype. An estimate of the proportion of cases caused by each mutation can be made, although there is an under representation of the occurrence of the most common mutations since diagnostic laboratories generally publish or submit novel mutations only to the database. 69 sequence variants that have been found in the course of sequencing NCL genes diagnostically are also listed in this database. Correlations between genotype, phenotype and morphological changes in patients have been reviewed previously [27] [28]. It is important to know these correlations as new treatments that do not fully compensate for the genetic defect may reduce but not completely eliminate the disease burden.

The number of families with NCL that remain unsolved at the DNA level used to be estimated at 10% of cases. This must be decreasing due to the advances in DNA sequencing technology being applied both to current and to historical samples, and to comprehensive genetic diagnoses becoming more widely available. The exact number of genes that can cause NCL remains uncertain. At least one family thought to represent *CLN9*, and associated

with disease of juvenile-onset, and specific cell characteristics, is now reclassified as a CLN5 variant [29]. However, the genetic basis in at least one other similar family has yet to be clarified [30]. The most recently identified genes are found only in single families, and whilst there is no disputing that these novel genes cause disease, it may be timely to revisit the criteria for a diagnosis of NCL. The new gene-based classification scheme for the NCLs [7] links with the most recent diagnostic algorithms that take into account these rare as well as more common genetic bases for NCL.

In conclusion, the expanding numbers of NCL genes combined with the recognition of the broader range of associated phenotypes is contributing to a fuller understanding of the molecular genetics of NCL. This genetic picture is considerably more complex than was first envisioned at the start of the genetic era of the NCLs.

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Abbreviations

NCL	Neuronal ceroid lipofuscinosis
EPMR	Epilepsy with progressive mental retardation
PME	Progressive myoclonic epilepsy

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Highlights

- Number of genes and mutations that cause NCL summarized
- Correlation between genotype and phenotype discussed
- Outlook on genotype and phenotype presented
- Knowledge of encoded proteins summarised

Table 1

Summary of the identification of genes that cause NCL

Gene	Year of identification	Main approaches used for locus identification	Other approaches used	Reference
CLN1/PPT1	1995	Linkage	Linkage disequilibrium	[31]
CLN2/TPP1	1997	Biochemical	Linkage	[32]
CLN3	1995	Linkage	Linkage disequilibrium	[33]
CLN4/DNAJC5	2011	Linkage, Exome sequencing	Gene expression	[1]
CLN5	1998	Linkage	Linkage disequilibrium	[34]
CLN6	2002	Linkage	Homozygosity mapping	[35]
CLN7/MFSD8	2007	Linkage	Homozygosity mapping	[36]
CLN8	1999	Linkage, Animal model	Homozygosity mapping	[8]
CLN9	Not known			
CLN10/CTSD	2006	Animal model		[37] [38]
CLN11/GRN	2012	Linkage, Exome sequencing		[10]
CLN12/ATP13A2	2012	Exome sequencing		[21]
CLN13/CTSF	2012	Linkage, Exome sequencing		[39]
CLN14/KCTD7	2012	Exome sequencing		[17]

Table 2

Correlation between genotype and phenotype in NCL cases

Gene	No. mutations	Widespread common mutations	Country-specific mutations	Genotype-phenotype correlation*
CTSD/CLN10	8	Not known	Not known	**Congenital** Late infantile Juvenile Adult
PPT1/CLN1	67	p.Arg122Trp p.Arg151X	p.Thr75Pro and p.Leu10X in Scotland	**Infantile** Late infantile Juvenile Adult
TPP1/CLN2	116	c.509-1G>C p.Arg208X	p.Glu284Val in Canada	**Late infantile** Juvenile Protracted *SCAR7*
CLN3	67	1 kb intragenic deletion in Caucasian populations	1 kb deletion in many countries 2.8 kb intragenic deletion in Finland	Juvenile Protracted *Autophagic vacuolar myopathy* *Retinitis pigmentosa* *Cone-rod dystrophy*
CLN5	36	None	p.Tyr392X and p.Trp75X in Finland	**Late infantile** Juvenile Protracted Adult
CLN6	71	None	p.Ile154del in Portugal	**Late infantile** Protracted Adult Kufs type A *Juvenile cerebellar ataxia* *Teenage progressive myoclonic epilepsy*
MFSD8/CLN7	38	None	P.Thr294Lys in Roma Gypsies; c.724+2T>A in Eastern Europe	**Late infantile** Juvenile protracted *Macular dystrophy* *Cone-rod dystrophy*
CLN8	31	None	p.Arg24Gly in Finland causing EPMR p.Arg204Cys and pTrp263Cys in Turkey	**Late infantile** protracted ***zEPMR/Northern epilepsy***
CLN4/DNAJC5	2	p.Leu116del p.Leu115Arg	N/A	Adult autosomal dominant (Parry disease)
CLN11/GRN	2+	N/A	N/A	**Adult** *Frontotemporal lobar dementia (when heterozygous)*
CLN12/ATP13A2	1−	N/A	N/A	**Juvenile** ***Kufor-Rakeb syndrome***
CLN13/CTSF	6	N/A	N/A	**Adult Kufs type B**
CLN14/KCTD7	1$	N/A	N/A	**Infantile** ***Progressive myoclonic epilepsy-3*** ***Opsoclonus-myoclonus ataxia-like syndrome***
SGSH	2^	N/A	N/A	Adult ***Late infantile MPSIIIA***
CLCN6	2*a*	Not known	Not known	Adult (only found in heterozygous form to date)

* bold = phenotype caused by complete loss of gene function

italics – non-NCL disease phenotype that in some cases may be more typically associated with this gene

[+] only the mutation that causes NCL when present on both disease alleles is indicated; this mutation, and other mutations in this gene, cause later onset frontotemploral lobar dementia when present in heterozygous form

[–] only the mutation that causes NCL is indicated; this mutation, other mutations cause Kufor-Rakeb syndrome

[$] only the mutation that causes NCL is indicated; this mutation, other mutations cause PME-3 or opsoclonus-myoclonus ataxia-like syndrome

[^] only the mutations described in a patient diagnosed with NCL are indicated; all other known mutations cause MPSIIIA

[a] these mutations in *CLCN6* may modify disease phenotype

Table 3

Summary of mutation and sequence variants in NCL genes contained within the NCL Mutation Database (May 2015)

Gene	CLN1	CLN2	CLN3	CLN4	CLN5	CLN6	CLN7	CLN8	CLN10	CLN11	CLN12	CLN13	CLN14	Grand total
Total changes	76	140	80	2	46	75	40	33	13	2	1	6	1	515
Mutations	67	116	67	2	36	71	38	31	8	2	1	6	1	446
Sequence variations	9	24	13	–	10	4	2	2	5	–	–	–	–	69
Missense	29	53	19	1	16	38	21	20	6	0	1	4	1	209
Nonsense	11	16	14	–	8	9	7	1	1	1	–	–	–	68
Small deletions	7	14	9	1	8	9	1	5	1	1	–	–	–	56
Small insertion or duplication	5	8	6	–	3	4	–	–	–	–	–	1	–	27
Splice defects	11	17	15	–	–	6	8	1	4	–	–	1	–	63
Large deletions	1	1	4	–	1	1	–	4	0	–	–	–	–	12
Large insertions	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Delins	1	2	–	–	–	3	1	–	–	–	–	–	–	7
Promoter change	3	4	2	–	–	2	–	–	–	–	–	–	–	11
3′ UTR changes	2	1	–	–	–	–	–	–	–	–	–	–	–	3
Initiation site change	1	–	–	–	–	–	–	–	–	–	–	–	–	1
No. of patients	220	369	423	7	89	132	91	74	15	3	4	7	2	1436
No. of families	167	347	396	7	81	112	73	69	11	2	1	4	1	1271

* Only data that causes NCL is included (see Table 2)

∞ small deletions/insertions are < 100 b. Large deletions/insertion are > 100 b.

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