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Review

Genetics of the neuronal ceroid lipofuscinoses (Batten disease)☆

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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: “Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease).”

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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 summarize 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 permit massively parallel sequencing of the whole exome in a relatively short space of time have 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

Abbreviations: NCL, Neuronal ceroid lipofuscinosis; EPMR, Epilepsy with progressive mental retardation; PME, Progressive myoclonic epilepsy

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

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, remain 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 recognized 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 recognized 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 *CLN6* gene. Another family has been described in which a single mutation in *CLN6* is the

Table 2
Correlation between genotype and phenotype in NCL cases.

Gene	No. mutations	Widespread common mutations	Country-specific mutations	Genotype-phenotype correlation ^a
<i>CTSD/CLN10</i>	8	Not known	Not known	Congenital Late infantile Juvenile Adult
<i>PPT1/CLN1</i>	67	p.Arg122Trp p.Arg151*	p.Thr75Pro and p.Leu10* in Scotland	Infantile Late infantile Juvenile Adult
<i>TPP1/CLN2</i>	116	c.509-1G>C p.Arg208*	p.Glu284Val in Canada	Late infantile Juvenile Protracted SCAR7
<i>CLN3</i>	67	1 kb intragenic deletion in Caucasian populations	1 kb deletion in many countries 2.8 kb intragenic deletion in Finland	Juvenile Protracted <i>Autophagic vacuolar myopathy</i> <i>Retinitis pigmentosa</i> <i>Cone-rod dystrophy</i>
<i>CLN5</i>	36	None	p.Tyr392* and p.Trp75* in Finland	Late infantile Juvenile Protracted Adult
<i>CLN6</i>	71	None	p.Ile154del in Portugal	Late infantile Protracted Adult Kufs type A <i>Juvenile cerebellar ataxia</i> <i>Teenage progressive myoclonic epilepsy</i>
<i>MFSD8/CLN7</i>	38	None	P.Thr294Lys in Roma Gypsies; c.724+2T>A in Eastern Europe	Late infantile Juvenile protracted <i>Macular dystrophy</i> <i>Cone-rod dystrophy</i>
<i>CLN8</i>	31	None	p.Arg24Gly in Finland causing EPMR p.Arg204Cys and p.Trp263Cys in Turkey	Late infantile Protracted <i>EPMR/Northern epilepsy</i> Adult autosomal dominant (Parry disease)
<i>CLN4/DNAJC5</i>	2	p.Leu116del p.Leu115Arg	N/A	Adult <i>Frontotemporal lobar dementia (when heterozygous)</i>
<i>CLN11/GRN</i>	2 ^b	N/A	N/A	Juvenile <i>Kufor–Rakeb syndrome</i>
<i>CLN12/ATP13A2</i>	1 ^c	N/A	N/A	Adult Kufs type B Infantile Progressive myoclonic epilepsy-3 Opsoclonus-myoclonus ataxia-like syndrome
<i>CLN13/CTSF</i> <i>CLN14/KCTD7</i>	6 ^d 1 ^d	N/A N/A	N/A N/A	Adult Late infantile MPSIIIA Adult (only found in heterozygous form to date)
<i>SGSH</i>	2 ^e	N/A	N/A	
<i>CLCN6</i>	2 ^f	Not known	Not known	

^a 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.

^b 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 frontotemporal lobar dementia when present in heterozygous form.

^c Only the mutation that causes NCL is indicated; other mutations cause Kufor–Rakeb syndrome.

^d Only the mutation that causes NCL is indicated; other mutations cause PME-3 or opsoclonus-myoclonus ataxia-like syndrome.

^e Only the mutations described in a patient diagnosed with NCL are indicated; all other known mutations cause MPSIIIA.

^f These mutations in *CLCN6* may modify disease phenotype.

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 recognized group of experts at the next international congress to be held in 2016, following the working pattern already established

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 cause NCL are included (see Table 2)

Small deletions/insertions are < 100 b. Large deletions/insertion are > 100 b.

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 or by personal communication to the curator 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 while 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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