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Review

Genetic basis and phenotypic correlations of the neuronal ceroid lipofusinoses ☆

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ABSTRACT

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited neurodegenerative disorders that mainly affect children and are grouped together by similar clinical features and the accumulation of autofluorescent storage material. More than a dozen genes containing nearly 400 mutations underlying human NCLs have been identified. Most of the mutations in these genes are associated with a typical disease phenotype, but some result in variable disease onset, severity and progression. There are still disease subgroups with unknown molecular genetic backgrounds. This article is part of a Special Issue entitled: The Neuronal Ceroid Lipofuscinoses or Batten Disease.

The common clinical features of the neuronal ceroid lipofuscinoses are 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. Mutations in more than a dozen genes have now been described in families diagnosed with NCL disease (Table 1). Many of the genes that cause typical NCL disease with onset in childhood have been identified, and in very recent years the genetic basis of many of the later onset cases has been delineated, including the dominant adult onset NCL disease. However, there remain families diagnosed with NCL of all ages of onset in which the underlying genetic cause has not been described. Mutations in other genes that cause NCL-like disease in animals do not appear to be a main cause of NCL in these remaining cases.

The aim of this review is to briefly summarize the genetic basis of NCL and correlations with disease phenotype in a readily accessible and useful format. Further details can be found in the recently expanded NCL mutation database (http://www.ucl.ac.uk/ncl).

Since the late 1960s NCL disease has been divided broadly into four ages of onset: infantile, late infantile, juvenile and adult, leading to the initial simple supposition that there are four genes responsible for NCL disease, *CLN1*, *CLN2*, *CLN3* and *CLN4*, respectively. The first three were the initial NCL genes to be identified, and many more were described before *CLN4* was found. Genes carrying mutations that cause NCL have been discovered by a variety of experimental approaches, largely reflective of the available technology at the time of identification (Table 1). The first genes were discovered in 1995 by applying classic and time-consuming genetic linkage approaches to large numbers of similarly affected families followed by positional cloning of the genes (*CLN1*/*PPT1* and *CLN3*). In contrast, *CLN2*/*TPP1* was identified using a biochemical approach to detect mannose-6-phosphate tagged lysosomal enzymes and subsequently identifying one that was absent in a patient. As sequencing of the human genome progressed and was completed, allowing more informative sequence variants to be identified, fewer families were required to provide sufficient power for genetic linkage. This was especially relevant when recognition of the stretches of homozygosity that are present in consanguineous families was used to narrow down the candidate gene region. These advances allowed the identification of genes responsible for increasingly smaller proportions of cases (e.g. *CLN5*, *CLN6*, *CLN7*/*MFSD8*, *CLN8*). Finally, the most recent identification of NCL disease gene has used the latest sequencing technology that permits massively parallel sequencing of the whole exome in a relatively short space of time and allows the identification of the disease gene in single families (e.g. *CLN4*/*DNAJC5*, *CLN11*/*GRN*, *CLN12*/*ATP13A2*, *CLN13*/*CTSF*, *CLN14KCTD7*).

All NCL genes so far identified lie on autosomes and, in most cases, disease is inherited in a recessive manner, being caused when there are deleterious mutations in both disease gene alleles. There are two notable exceptions or points of interest: (1) the dominant inheritance for adult onset NCL caused by mutations in *CLN4*/*DNAJC5* [1]; (2) A patient

Abbreviations: NCL, Neuronal ceroid lipofuscinosis; EPMR, progressive epilepsy with mental retardation

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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
CLN1/PPT1	1995	Linkage	Linkage disequilibrium	[17]
CLN2/TPP1	1997	Biochemical	Linkage	[18]
CLN3	1995	Linkage	Linkage disequilibrium	[19]
CLN4/DNAJC5	2011	Linkage, Exome sequencing	Gene expression	[1]
CLN5	1998	Linkage	Linkage disequilibrium	[20]
CLN6	2002	Linkage	Homozygosity mapping	[21]
CLN7/MFSD8	2007	Linkage	Homozygosity mapping	[22]
CLN8	1999	Linkage, Animal model	Homozygosity mapping	[23]
CLN9	Not known			
CLN10/CTSD	2006	Animal model		[24,25]
CLN11/GRN	2012	Linkage, Exome sequencing		[4]
CLN12/ATP13A2	2012	Exome sequencing		[10]
CLN13/CTSF	2012	Linkage, Exome sequencing		[26]
CLN14/KCTD7	2012	Exome sequencing		[6]

with complete isodisomy of chromosome 8, leading to homozygosity of a maternally-inherited deletion in *CLN8* [2]. This is the only published report of uniparental disomy in the NCLs.

For most NCL genes there is a known typical disease phenotype associated with complete loss of function (Table 2) but there is also often disease that is more protracted or has a later age of onset when mutations are presumed to have 'milder' effects on gene function. In contrast, similar NCL disease can be caused by mutations in several genes (e.g. late infantile variant NCL can be caused by mutations in *CLN5*, *CLN6*, *CLN7*, or *CLN8*). This has led to the recognition of the need for a new classification system that is genetically based but takes into account these significant phenotypic consequences, and its development and subsequent clinical auditing [3].

There are also an increasing number of instances where different mutations in a single gene can give rise to different diseases (Table 2), such as: (1) CLN8 disease where different recessive mutations lead to quite different disease including progressive epilepsy with mental retardation (EPMR). Indeed EPMR was the first disease identified caused by mutations in this gene; (2) recessive CLN11 disease caused by mutations in *GRN*, since heterozygous mutations in *GRN* are a major cause of frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), the second most common type of early-onset dementia. One family homozygous for a frameshift mutation was diagnosed with NCL disease, consistent with the rectilinear profiles typical of NCL recently recognized in progranulin-deficient mice [4]. The age-at-onset and neuropathology of FTLD-TDP and NCL are markedly different and represent the long suspected link that may exist between the rare NCL and a common neurological disorder; (3) CLN3 disease, where the most common and very widespread mutation in the *CLN3* gene, a 1 kb deletion, may not cause total loss of CLN3 function, leading to the hypothesis that disease caused by complete loss of function has not been recognized or is lethal, and that disease associated with mutations in this gene could have a much wider phenotype than currently accepted [5]; (4) CLN4 disease, includes the only autosomal dominant type of NCL, although disease caused by complete loss of CLN4 function is not known, though animal models would predict very severe and early onset disease; (5) CLN14 disease, since mutations in *CLN14/KCTD7* have now been reported to cause three different diseases [6–9]; (6) CLN12 disease, in one family diagnosed with NCL, albeit recognized as atypical [10], whereas all other mutations in *CLN12/ATP13A2* cause Kufor–Rakeb syndrome; (7) a case diagnosed with adult onset NCL that was found to have mutations in *SGSH* which usually underlies the late infantile onset disease mucopolysaccharidosis type IIIA (MPSIIIA) [11].

Many of the mutations in NCL genes are more common in certain populations, probably representing a local founder effect, and a few are even more widespread across several continents, probably caused by an ancient founder effect (Table 2). The common mutation causing juvenile CLN3 disease is the best example of this. Whether this global spreading represents any genetic advantage is not known. In either instance diagnostic testing can be targeted to these common mutations.

There are an increasing number of reports of patients carrying changes in more than one NCL gene, although the contribution of these sequence variations to their disease phenotype is not clear. For example, two unrelated patients were described who carry single mutations in the *CLCN6* gene, but one of these patients was later found to be compound heterozygous for mutations in *CLN5*. In both families, the *CLCN6* carrier parents did not have the same disease phenotype as their affected offspring. Since a mouse model lacking *CLCN6* clearly has an NCL-like disease this gene is included in Table 2. Similarly some patients carry mutations in more than one gene that underlie variant late infantile NCL (e.g. changes in *CLN5* have been found alongside those in *CLN6* or *CLN7* or *CLN8*). These may be examples in the NCLs of a mutation or specific allele of one gene enhancing or ameliorating the disease phenotype.

There are several intriguing reports that implicate NCL genes in a wider biology of disease: (1) One patient with disease that presented shortly after birth was found to carry heterozygous mutations in CLN5, which would normally have been expected to cause disease that began in late infancy, together with a mutation in POLG1 that acts to maintain mitochondrial DNA integrity, suggesting that this combination of mutations resulted in a markedly modified disease course [12]. (2) Increased expression of CLN8 may act as a modifier of Gaucher disease [13]. (3) A study of somatic mutations acquired in human cancer cells (COSMIC) has revealed changes in all known NCL genes (*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/) [14] and it is postulated that some of these may confer a growth advantage to these cells.

Several genes have been identified recently as a result of the advances in DNA sequencing technology. This new technology will no doubt present more new NCL genes in the future, and whilst the gene identification will not be in doubt, a diagnosis using well defined criteria may become increasingly important to be sure that the disease falls within the NCL family of diseases. Thus, some patients diagnosed with NCL may turn out to really have atypical forms of other diseases, such as cases diagnosed with NCL but caused by mutations in *SGSH*. However, in other cases it may be that the distinction between disease phenotypes is not so clear cut, such as the family diagnosed with NCL carrying mutations in *CLN13/ATP13A2*.

One gene that is not included in the tables is *CLCN7* which, like some other genes, causes disease that has similarities to NCL in mice but in humans is only known to cause the severe autosomal recessive disease infantile malignant osteopetrosis. Since patients develop blindness and CNS degeneration even when the osteopetrosis is treated with bone marrow transplantation, specific mutations or alleles in this gene may also cause NCL-like disease or modify that caused by mutations in other genes, as suggested for *CLCN6*.

Table 2
Correlation between genotype and phenotype in NCL cases.

Gene	No. mutations	Widespread common mutations	Country-specific mutations	Genotype–phenotype correlation[a]
CTSD/CLN10	7	Not known	Not known	**Congenital** Late infantile Juvenile Adult
PPT1/CLN1	64	p.Arg122Trp p.Arg151X	p.Thr75Pro and p.Leu10X in Scotland	**Infantile** Late infantile Juvenile Adult
TPP1/CLN2	105	c.509-1G>C p.Arg208X	p.Glu284Val in Canada	**Late infantile** Juvenile Protracted
CLN3	57	1 kb intragenic deletion in Caucasian populations	1 kb deletion in many countries 2.8 kb intragenic deletion in Finland	Juvenile Protracted
CLN5	36	None	p.Tyr392X and p.Trp75X in Finland	**Late infantile** Juvenile Protracted Adult
CLN6	68	None	p.Ile154del in Portugal	**Late infantile** Protracted Adult Kufs type A
MFSD8/CLN7	31	None	P.Thr294Lys in Roma Gypsies; c.724+2T>A in Eastern Europe	**Late infantile** Juvenile protracted
CLN8	24	None	p.Arg24Gly in Finland causing EPMR p.Arg204Cys and pTrp263Cys in Turkey	**Late infantile** Protracted **EPMR/Northern epilepsy**
CLN4/DNAJC5	2	p.Leu116del p.Leu115Arg	N/A	Adult autosomal dominant
CLN11/GRN	1[b]	N/A	N/A	**Adult** *Frontotemporal lobar dementia (when heterozygous)*
CLN12/ATP13A2	1[c]	N/A	N/A	**Juvenile** **Kufor–Rakeb syndrome**
CLN13/CTSF	5	N/A	N/A	**Adult Kufs type B**
CLN14/KCTD7	1[d]	N/A	N/A	**Infantile** **Progressive myoclonic epilepsy-3** **Opsoclonus-myoclonus ataxia-like syndrome**
SGSH	2[e]	N/A	N/A	Adult **Late infantile MPSIIIA**
CLCN6	2[f]	Not known	Not known	Adult (only found in heterozygous form to date)

[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; this mutation, other mutations cause Kufor–Rakeb syndrome.
[d] Only the mutation that causes NCL is indicated; this mutation, 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.

Table 3
Summary of mutation and sequence variants in NCL genes contained within the NCL Mutation Database (Jan 2013).

Gene	CLN1	CLN2	CLN3	CLN4	CLN5	CLN6	CLN7	CLN8	CLN10	CLN11	CLN12	CLN13	CLN14	Grand total[a]
Total changes	73	129	70	2	45	72	33	26	12	1	1	5	1	471
Mutations	64	105	57	2	36	68	31	24	7	1	1	5	1	403
Sequence variations	9	24	13	–	9	4	2	2	5	–	–	–	–	68
Missense	27	48	13	1	16	37	17	19	7	0	1	4	1	189
Nonsense	11	16	12	–	8	8	6	–	1	–	–	–	0	63
Small deletions[b]	7	12	8	1	8	9	1	5	1	1	–	–	–	53
Small insertion or duplication[b]	4	6	5	–	3	4	–	–	–	–	–	1	–	23
Splice defects	11	15	14	–	–	6	6	–	4	–	–	–	–	56
Large deletions[b]	1	1	4	–	1	1	–	2	0	–	–	–	–	10
Large insertions[b]	–	–	–	–	–	–	–	–	–	–	–	–	–	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. patients	216	326	403	7	85	125	73	70	11	2	4	4	2	1329
No. families	163	317	383	7	79	106	65	65	10	1	1	3	1	1202

[a] Only data that causes NCL is included (see Table 2).
[b] Small deletions/insertions are <100 b. Large deletions/insertion are >100 b.

All known mutations and sequence variations in NCL genes are listed in the NCL Mutation Database (http://www.ucl.ac.uk/ncl) (Table 3). 403 mutations that cause NCL are currently known. This NCL Mutation Database has recently been updated to also include the genetic basis of NCL disease in patients and families reported in clinical or scientific publications to allow better correlation between gene changes and disease phenotype. This of course leads to an under representation of the occurrence of the most common mutations since diagnostic laboratories tend to submit novel mutations only to the database. 69 sequence variants are also listed in this database that generally reflect those that have been found in the course of sequencing NCL genes diagnostically and so will be an underestimate. Correlations between genotype, phenotype and morphological changes in patients have been reviewed previously [15,16].

The exact number of NCL genes is still uncertain, and not just because some families do not have a genetic diagnosis. Although numerically *CLN14* has been reached (albeit without an identity for *CLN9*), mutations that cause NCL in some of the most recently identified genes are found only in single families. 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 NCL [3] leads readily into updating diagnostic algorithms that take into account these rare as well as more common genetic bases for NCL. Genes remaining to be identified include those causing the so-called 'CLN9' variant which causes disease of juvenile onset, and also cases still of late infantile onset and adult onset.

In conclusion, a full understanding of the molecular genetics of NCL is nearer with the recent identification of four new genes in families diagnosed with NCL, and especially the further delineation of the genetic cause of adult onset NCL. Certainly the genetic picture is more complex than was first envisioned in the 1990s, and even five years ago. The connection between the function of each gene, the disease phenotype and the characteristic autofluorescent storage material is still not fully established. However, the continued study of NCL genes at both a cellular level and in model organisms should lead eventually to a fuller understanding.

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