Progress towards understanding the neurobiology of Batten disease or neuronal ceroid lipofuscinosis
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Purpose of review
The identification of genes mutated in the neuronal ceroid lipofuscinosis has accelerated research into the mechanisms that underlie these fatal autosomal recessive storage disorders, which are often referred to as Batten disease. This review summarizes progress in this field since October 2001, describing advances in cell biology, the characterization of new animal models of neuronal ceroid lipofuscinosis, and the impact of novel methodology to reveal insights into its pathogenesis.

Recent findings
Gene products for six of the eight forms of neuronal ceroid lipofuscinosis have now been discovered, and concerted efforts are underway to understand the normal biology of each gene product and how this may be altered by mutation. Several lines of evidence point to functions for the CLN genes in the endosomal–lysosomal system, and suggest neuron-specific roles for these proteins. Indeed, a requirement for appropriate protein trafficking within neurons may explain the profound and selective effects of these disorders upon the central nervous system. The development of mouse and large animal models has enabled comparative studies of the progressive effects of disease, including characterization by morphological and biochemical means supplemented by metabonomic and microarray techniques.

Summary
Insights into disease mechanisms are building a detailed profile of the impact of neuronal ceroid lipofuscinosis upon the brain. With the eventual aim of developing successful therapeutic strategies, it will be equally important to characterize the clinical progression of the disorder, and to identify quantifiable endpoints that can ultimately be used in clinical trials.

Keywords
lysosomal storage disorders, neurodegeneration, neuronal ceroid lipofuscinosis, pathologica1 mechanisms

Abbreviations
ANCL adult neuronal ceroid lipofuscinosis
CNS central nervous system
GABA α-aminobutyric acid
GAD65 glutamic acid decarboxylase
INCL infantile neuronal ceroid lipofuscinosis
JNCL juvenile neuronal ceroid lipofuscinosis
LINCL late infantile neuronal ceroid lipofuscinosis
NCL neuronal ceroid lipofuscinosis
PPT palmitoyl-protein thioesterase
TPP-1 tripeptidyl peptidase-1

Introduction
The neuronal ceroid lipofuscinoses (NCLs) are a significant cause of childhood progressive intellectual and neurological deterioration [1]. Collectively, this group of at least eight genetically distinct disorders is considered the most common pediatric neurodegenerative disease. Originally described as a form of ‘amaurotic familial idiocy’, these fatal disorders were subsequently renamed because of the characteristic intracellular accumulation of ceroid and lipofuscin. The precise relationship between the appearance of these lipopigments and cellular dysfunction remains unclear, but these disorders exert a profound effect upon the central nervous system (CNS) of affected individuals [2,3]. The substantial impact of the NCLs upon carers has only recently begun to be evaluated [4].

As comprehensively reviewed elsewhere, the NCLs are typified by their progressive nature, presenting with visual disturbances leading to blindness, neurocognitive decline, an increased severity of untreatable seizures and ultimately premature death [2,3,5,6]. The vast majority of cases manifest during childhood with an infantile (INCL), late infantile (LINCL) or juvenile (JNCL) onset; although rare adult onset forms (ANCL) and an increasing number of variant forms are also recognized. This spectrum of NCL subtypes makes accurate diagnosis complicated, relying on combined histological, ultrastructural and enzymatic criteria, together with subtle differences in clinical presentation [5–7]. As with all fatal genetically predetermined disorders, counselling is of great importance for newly diagnosed families, and parents’ organizations play an invaluable role providing support and information (www.bdsra.org and www.bdfauk.org.uk).

Genotyping is the definitive means of distinguishing between forms of NCL, although enzymatic analysis is
informative as a first approach [2,6,8,9]. Since 1995 the individual genes mutated in six forms of NCL have been identified [5,8]. The products of these ‘CLN’ genes fall into two distinct categories comprising either soluble lysosomal enzymes (CLN1 and CLN2) [10] or predicted transmembrane proteins of unknown structure and function (CLN3, CLN5, CLN6 and CLN8). A comprehensive catalogue of mutations in each gene has been compiled and is available online (www.ucl.ac.uk/ncl), facilitating the establishment of phenotype–genotype correlations [2,9,11].

Despite the identification of their molecular basis, very little is known about how mutations in these different genes ultimately result in this profoundly disabling disorder. This is particularly true for CLN3, CLN5, CLN6 and CLN8, in which basic knowledge of the normal roles of these proteins, and how their functions are compromised by mutation, is incomplete. Indeed, many significant questions about the pathological mechanisms that operate in the NCLs remain unanswered. Why is it that mutations in so many different genes result in similar pathological profiles, albeit with different ages of onset and rates of progression? Moreover, why are the effects of these mutations largely confined to the CNS when autofluorescent lipopigments accumulate throughout the body?

This review focuses on recent progress towards understanding the neurobiology of the NCLs, highlighting the latest advances in cell biology, and the impact of new animal models and novel methodology to provide a fresh perspective on disease mechanisms. As a clearer picture of the pathological events in the NCLs emerges, attention will turn towards therapeutic attempts to halt disease progression. To be successful it will require a detailed knowledge of clinical progression together with a series of quantifiable endpoints to judge therapeutic efficacy.

**Progress in identifying mutated genes**

The most recently identified CLN gene is *CLN6*, which is mutated in variant LINCL [12**,13**]. *CLN6* is conserved across vertebrates, and encodes a novel 311 amino acid protein that is predicted to be an integral membrane protein with six or seven transmembrane domains. Mutational analysis of affected families revealed at least six different mutations, the majority of which result in the introduction of a premature stop codon. Sequencing of the orthologous gene in the *nclf* mouse revealed a frameshift truncation, which is replicated in three families of Pakistani origin [13**]. *CLN6* is also predicted to be orthologous to NCL-causing genes in both South Hampshire and Merino sheep [14,15], although the precise mutation in each sheep model remains unidentified.

At present, the gene loci of the two remaining unidentified forms of NCL remain elusive. The gene locus for Turkish variant LINCL (*CLN7*) remains unidentified, but may be allelic to *CLN8* [16]. Efforts to isolate the proposed *CLN4* gene mutated in ANCL or Kufs disease have been unsuccessful. However, mutations in other NCL-causing genes that leave some functionally active gene product may be responsible for certain delayed onset forms of NCL [17,18]. However, it is unlikely that this explanation holds true for all forms of ANCL, especially the rarer autosomal dominant form or Parry disease [19].

**The cell biology of neuronal ceroid lipofuscinoses involving soluble lysosomal enzymes**

The *CLN1* gene encodes a palmitoyl-protein thioesterase-1 (PPT1), a soluble lysosomal hydrolase that cleaves long-chain fatty acid side chains from proteins [6,10]. Several lines of evidence support the lysosomal nature of PPT1 function, most recently via the effects of lysosomotropic agents upon the accumulation of lipid thioesters in PPT1-deficient lymphoblasts [20*]. The appearance of lipid thioesters in the lysosomal fraction is blocked by inhibitors of lysosomal proteolysis, including cysteamine, suggesting that the effects of this proposed therapeutic agent may be more complex than previously thought [20*].

In contrast, a non-lysosomal localization of transfected PPT1 has been reported in mouse primary neurons and fractionated mouse brain, co-localizing with markers of synaptosomes and synaptic vesicles [21*] and PPT1 is targeted preferentially to axons, colocalizing with microtubule associated protein-1 [22]. These data have been interpreted as evidence that PPT1 may play a crucial role outside lysosomes in the brain and may be associated with synaptic function. Interestingly, the subcellular localization of PPT1 is redistributed with kainic acid-induced status epilepticus, not only enhancing co-localization with presynaptic membrane markers but also inducing the prolonged localized upregulation of PPT1 expression [23]. Taken together, these data suggest further roles for PPT1 in protecting neurons from excitotoxicity and in synaptic plasticity.

The *CLN2* gene encodes tripeptidyl peptidase-1 (TPP-1), which cleaves triptides from the N-terminus of small proteins before their degradation by other lysosomal proteases [10]. The biochemical and immunohistochemical mapping of TPP-1 distribution reveals variable, but widespread, expression in both somatic and nervous tissue, although TPP-1 activity and protein levels are not always correlated [24,25]. Until recently very little was known about the natural substrates of TPP-1, but emerging evidence indicates that TPP-1 is essential for
the degradation of cholecystokinin-8 in the mouse brain [26]. Failure to degrade neuropeptides may have deleterious effects for neuronal function and survival. It is significant that outside the CNS a second peptidase can compensate for the loss of TPP-1, potentially explaining why non-neuronal tissues are spared [27*].

The cell biology of neuronal ceroid lipofuscinoses involving transmembrane proteins
The genes mutated in JNCL (CLN3) and Finnish variant LINCL (CLN5) both encode proteins that are predicted to reside in the lysosomal membrane [28], although emerging evidence suggests additional extralysosomal roles. As with PPT1, the expression of transfected and endogenous CLN3 is not exclusively lysosomal in neurons. The targeting of CLN3 to synapticosomes, although not synaptic vesicles themselves, implies that specific routes exist for the intracellular trafficking of CLN3 within neurons [29]. Characterization of the biosynthesis and intracellular location of transiently transfected CLN5 appears to confirm its lysosomal localization, with mutant forms of CLN5 retained within the Golgi complex [30]. The studies also revealed the secretion of a 60 000 MW glycosylated CLN5 peptide, suggesting that the use of different start methionines may produce both membrane-bound and soluble forms of this protein [30,31*].

The presence of each CLN protein within the endosomal–lysosomal system (CLN1, CLN2, CLN3, CLN5) and evidence that each are trafficked through, or are present in (CLN8), the endoplasmic reticulum–Golgi system, suggests that these gene products may compensate for the loss of TPP-1, potentially explaining why non-neuronal tissues are spared [27].

Cell death mechanisms
Recent evidence from other neurodegenerative disorders argues against exclusively apoptotic versus necrotic cell death, instead favouring a variety of cell death forms [33]. It is likely that the NCLs follow this pattern with a spectrum of cell death events, although mechanistic observations have only been made in JNCL [34] and the mechanisms that trigger cell death remain unclear. A proposed anti-apoptotic role for CLN3 has now been localized to domains clustered around the c terminus, with specific deletion mutants in highly preserved regions, resulting in slowed growth and susceptibility to etoposide-induced apoptosis in lymphoblasts [34]. The non-opioid analgesic flupirtine also prevents etoposide-induced apoptotic cell death in CLN3- and CLN2-deficient teratocarcinoma-derived cell lines [35], but remains untested in appropriate animal models. The observed upregulation of CLN3 in some forms of cancer [36] may lead to the discovery of other potential roles for CLN3 in regulating cell death, as has been suggested for PPT1 [37].

New mouse models of neuronal ceroid lipofuscinosis
PPT1 null mutant mice exhibit an NCL-like phenotype with widespread accumulation of autofluorescent lipopigments, a shortened lifespan, progressive motor abnormalities and spontaneous myoclonic seizures [38**]. These mice also exhibit regionally specific cortical atrophy, laminar disruption and profound loss of subpopulations of inhibitory interneurons in the cortex and hippocampus, with persisting neurons exhibiting a range of dendritic abnormalities and the loss of synaptic spines [39]. Although it has been suggested that PPT1 plays an essential role in neuronal development and growth, initial studies suggest little effect of a lack of PPT1 on the developing CNS. A more detailed analysis may reveal subtle effects, but PPT1 appears to play a role in the maintenance of certain neuronal populations rather than during their development.

A third mouse model of JNCL has also become available, using a knock-in strategy to replicate the approximately 1 kb deletion in the CLN3 gene present in the majority of JNCL patients [40**]. These CLN3<sup>Δex7/8</sup> mice exhibit an NCL-like phenotype at an earlier age than previous CLN3 null mutant models, with widespread accumulation of autofluorescent lipopigments, motor abnormalities and shortened lifespan [40**]. Pathological changes within the CNS of CLN3<sup>Δex7/8</sup> mice are present prenatally, challenging the notion that JNCL only exerts its effect after a period of normal development. A detailed characterization of CLN3<sup>Δex7/8</sup> mice may uncover more subtle JNCL phenotypes, but it is already apparent that the retina of these mice exhibit the loss of cone-associated markers [40**], whereas CLN3 null mutants exhibit remarkably mild retinal pathology [41], certainly compared with <i>mnd</i> and <i>nclf</i> mice [42]. As with other murine JNCL models, CLN3<sup>Δex7/8</sup> mice do not exhibit spontaneous seizures, but may show an altered threshold to seizure induction as described in CLN3 null mutant mice [43].

The discovery that the <i>mnd</i> mouse bears a mutation in the <i>CLN8</i> gene [8], has seen a resurgence of studies in this model. <i>Mnd</i> mice exhibit a complex series of changes in the expression of glutamate receptor expres-
sion [44]. Most notable is the increased expression of the GluR2 subunit of the \(\alpha\)-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor, suggesting a compensatory change in response to elevated glutamate levels, which has been demonstrated by metabolic profiling [45**]. Progress has also been made towards providing functional and behavioural landmarks of disease progression. Presymptomatic \(mnd\) mice are hyperactive, more aggressive than controls, and display poor contextual and cued memory [46], recapitulating at least some of the behaviours seen in patients. Investigations of seizure susceptibility in both \(mnd\) and \(nclf\) mice revealed findings similar to CLN3 null mutant mice, but with seizure phenotypes strikingly different from controls (Pearce, personal communication).

**Clues about pathogenesis from other mutant mice**

Inactivation of a second lysosomal thioesterase, PPT2, produces a mild form of the PPT1 null mutant phenotype [38**], suggesting that PPT2 plays a role in the brain not carried out by PPT1. Surprisingly, chloride channel-3 null mutant mice also exhibit an aggressive NCL-like phenotype, which closely resembles that of cathepsin-D-deficient mice [47**], including retinal degeneration and reduced brain size [48]. Among other roles, chloride channels act to regulate the ionic composition of intracellular compartments and thus their pH [49]. Certainly, chloride channel-3 mutants also exhibit impaired acidification of synaptic vesicles, which has direct implications for neurotransmitter uptake [48]. As such, it may be significant that mutations of all CLN proteins except CLN2 and CLN8 have demonstrable effects upon pH within the endosomal–lysosomal system [50]. Furthermore, compounds that affect the pH of acidic intracellular compartments also appear to alter maturation of the TPP-1 proenzyme within lysosomes [51].

**Applying new methodology and learning new perspectives**

Novel methodologies that permit the simultaneous assessment of multiple gene or protein expression can provide powerful insights into disease mechanisms. High-density oligonucleotide microarrays have been used to examine changes in gene expression in the cerebellum of CLN3 null mutant mice [52*]. Bioinformatic analysis revealed more than twofold changes in the gene expression of 330 genes, which can be ascribed to a variety of functional groups (full data set available at www.urmc.rochester.edu/research/FGC/resource.html), most notably the upregulation of genes associated with an immune or inflammatory response and in the regulation and utilization of glutamate [52*]. Metabonomic screening [53] has recently been used to generate a metabolic profile of \(mnd\) mice, revealing deficits of vitamin E in both serum and brain and abnormal levels of low-weight metabolites, suggesting their redistribution across intracellular compartments [45**]. Significantly, dietary vitamin E supplementation reversed some of the metabolic abnormalities, especially increasing phenylalanine in the CNS, but had no effect upon brain pathology [45**]. Lipid chromatography and quantitative mass spectroscopy reveal profound changes in the composition of membrane phospholipids in INCL, but not JNCL postmortem brains [54]. These changes reflect pathological changes in membrane composition that could contribute directly to disease progression, but it will be crucial to determine when in pathogenesis these events first occur.

**Gliial and neuroimmune responses in neuronal ceroid lipofuscinosis**

There is considerable evidence for the activation of glial cell populations in different forms of NCL. Autopsy material derived from individuals with different forms of NCL shows a consistent and regionally specific pattern of astrocytosis and microglial activation (Tyynela et al., unpublished data). Similar data can be obtained from null mutant mouse models, although the timing of glial reactivity in relation to neuronal pathology remains unclear. However, activated microglia in cathepsin-D null mutant mice appear to play an active pathological role via the release of nitric oxide [55]. As these mice exhibit an aggressive INCL-like phenotype, it will be important to determine whether similar mechanisms operate in models of NCL. Reactive changes in astrocyte populations are likely to exert a profound effect upon the local environment around neurons and directly influence neuronal activity and synaptic efficacy [56].

Individuals with JNCL and CLN3 null mutant mice have a circulating autoantibody to glutamic acid decarboxylase (GAD65) that inhibits this enzyme’s ability to convert glutamic acid to \(\gamma\)-aminobutyric acid (GABA) and results in the presynaptic elevation of glutamate [52*]. GAD65 autoantibodies are also present in an extended series of JNCL patients, but not in individuals with other lysosomal storage disorders [57]. These findings may have significant implications for excitotoxic mechanisms, and could explain the specific targeting of inhibitory interneurons in this disorder. However, it remains unclear whether the autoimmune response contributes to JNCL pathogenesis or is one of several epiphenomena. Nevertheless, the lysosome plays an active role in antigen presentation, a process that is apparently abnormal in other storage disorders [58]. Although CNS levels of IgGs are significantly elevated in CLN3 null mutant mice, it remains unclear how these macromolecules gain access to the CNS.
Large animal models of neuronal ceroid lipofuscinosis

Accurate large animal models will prove essential for assaying the biodistribution and efficacy of potential therapies as these become available. Naturally occurring sheep strains that exhibit recessive NCL-like disorders are the best characterized examples, especially at a biochemical level [14,15]. At least two of these strains appear to bear mutations in ONCL6, the ovine orthologue of CLN6; including the Merino flock that bears close resemblance to the more established South Hampshire model [14]. These ovine models also exhibit a characteristic loss of GABAergic interneurons [15]. A form of NCL has also been reported in Borderdale sheep that appears to be distinct from ONCL6, but still exhibits the accumulation of subunit c of mitochondrial ATPase [59], in contrast to the Swedish Landrace sheep that have a deficiency of cathepsin D and exhibit INCL-like storage material [60]. Introduction of the point mutation that causes this ovine form of NCL into the mouse cathepsin D molecule severely affects its activity, stability, processing and secretion [61].

Human neuronal ceroid lipofuscinosis pathology

Different forms of NCL share a distinct pattern of neuronal degeneration in the hippocampus, unlike that associated with temporal lobe epilepsies, with the heavy involvement of sectors CA2–CA4 but relative sparing of CA1 [62]. This regional specificity also extends to activated glia and immunohistochemically identified interneurons, which exhibit a graded severity of loss with the relative sparing of calretinin-positive interneurons across all regions (Tyynela¨ et al., unpublished data). The selective vulnerability of interneuron populations may reflect the differential buffering capacities of calcium-binding proteins [63], or a more fundamental and regionally specific property, as yet unidentified. These data closely mirror findings in murine and sheep models, further emphasizing the existence of common pathological themes maintained across species boundaries and different forms of NCL. There is also considerable value in combining modern morphological and molecular methods to revisit archival patient-derived material [64], although robust quantitative data from human material remain sorely lacking.

Towards therapy: following the clinical progression of the neuronal ceroid lipofuscinoses

Once the focus ultimately shifts towards testing therapies it will be essential that rigorously defined landmarks exist for following disease progression and judging therapeutic efficacy. Ongoing efforts have provided considerable information, with recent reports detailing altered visual performance [7,65], somatosensory evoked responses [66], sleep patterns [67] and hyperandrogenism [68] in different forms of NCL. Imaging studies will be particularly informative, especially when combined with functional markers, and represent a relatively non-invasive means to assay progressive and selective effects of the disorder upon the CNS [69,70]. The provision of readily quantifiable scales to score the clinical course of different forms of NCL will prove particularly valuable in defining specific endpoints in the design of clinical trials [71*].

At present, the therapeutic outlook for the NCLs remains bleak, and many ethical and technical challenges remain to be surmounted. With the advent of appropriate animal models the systematic testing of therapeutic interventions can now begin, although suitable models do not yet exist for all forms of NCL. Replacement of the missing enzyme may be an option, in INCL and LINCL, but problems of enzyme production and the method of delivery will need to be overcome. The recent encouraging results of gene therapy in reversing functional and pathological deficits in a mouse model of mucopolysaccharidosis type VII [72**] suggest that similar approaches may be appropriate in the NCLs [73]. Indeed, recent findings suggest that such viral mediated delivery may be feasible in LINCL [74*]. However, this approach will necessarily be limited to forms of NCL with deficits in soluble lysosomal enzymes. Hematopoietic stem cell transplantation is now not recommended for the treatment of INCL [75], but there is hope that transplanted neural stem cells may eventually be capable of replacing damaged neurons. However, as with other approaches, appropriate reagents and cell lines will need to be generated and rigorously tested before this potential may be realized.

Conclusion

Without a detailed understanding of the precise mechanisms that operate within each form of NCL, successful treatments for these fatal disorders will remain a distant prospect. The identification of gene products is now complete for the majority of different forms and has enabled the investigation of normal and pathological cell biology. Many issues remain to be resolved, but several lines of evidence point to the critical involvement of the lysosomal–endosomal system. Nevertheless, it will be vital to establish whether CLN gene products play other specific roles within the nervous system. The development of new animal models and the application of novel technologies is gradually creating a detailed picture of the progressive effects of disease. These efforts must be mirrored by the continued development of appropriate means to follow the clinical course in affected individuals.
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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


In this latest update to an ongoing survey of the causes underlying intellectual and neurological deterioration in childhood, out of a total of 406 cases the NCLs represent the largest disease category with 87 cases (16.5%), and the combined total for all storage disorders is 257 cases (63.3%).


The effects of a long-term progressive and ultimately fatal disorder such as the NCLs upon parents and carers have not previously been assessed quantitatively. In comparison with parents of children with epilepsy or cerebral palsy, the parents or carers of NCL sufferers were found to be less optimistic, and have significantly higher depression and anxiety scores.


13 Wheeler RB, Sharp JD, Schultz RA, et al. The gene mutated in variant late-infantile neuronal ceroid lipofuscinosis (CLN6) and in nclf mutant mice encodes a novel predicted transmembrane protein. Am J Hum Genet 2002; 70:537–542. These two studies report the cloning and initial mutational analysis of the CLN6 gene, which is mutated in a form of variant late infantile NCL that is particularly prominent in southern Mediterranean and South American families. Both groups provide evidence that the candidate gene FLJ20561 on chromosome 15q21–23 represents CLN6. Armed with this information, it will be possible to generate tools for investigating CLN6 function. Importantly, these findings also validate nclf mice, Merino and South Hampshire sheep as animal models of variant INCL.


20 Lu JY, Verkruyse LA, Hofmann SL. The effects of lysosomotropic agents on normal and INCL cells provide further evidence for the lysosomal nature of palmitoyl-protein thioesterase function. Biochim Biophys Acta 2002; 1583:35–44. See Ref [21**].

21 Lehtovirta M, Kytala A, Eskelinen EL, et al. Palmitoyl protein thioesterase (PPT) localizes into synaptosomes and synaptic vesicles in neurons: implications for infantile neuronal ceroid lipofuscinosis (INCL). Hum Mol Genet 2001; 10:69–75. These two papers present alternative, but not mutually exclusive, views on PPT localization and function. Ref. [20] provides compelling evidence for lysosomal function in lymphoblasts and also reveals data that suggest that cysteamine may not act directly to cleave thioester bonds. In contrast, the data in Ref. [21**] suggest that PPT1 has a synaptic localization in primary neurons. This may represent an example of cell-type specific sub-cellular localization for PPT1, and it will have significant implications for pathogenesis if PPT1 also proves to play a distinct functional role in neurons.


27 Bernardini F, Warburton MJ. Lysosomal degradation of cholecystokinin-(29–33)-amide in mouse brain is dependent on tripeptidyl peptidase-I: implications for the degradation and storage of peptides in classical late-infantile neuronal ceroid lipofuscinosis. Biochem J 2002; 366:521–529. It remains to be seen if neuropeptide accumulation plays a direct role in the disease process, but the identification of a role for TPP-1 in cholecystokinin degradation provides further insight into the neuron-specific nature of TPP-1 deficiency. In somatic tissues dipeptidyl peptidase-I is able to compensate for the lack of TPP function, but does not perform this role in the brain in which the expression of dipeptidyl peptidase-I is very low.


Bolivar VJ, Scott Ganus J, Messer A. The development of behavioral NCLs, but in this study demonstrated only incomplete reversal of metabolic consequences of gene mutation. Application of these techniques to mnd mice remains unproved for any of the NCL genes, but several lines of evidence converge upon the potential for such a therapeutic strategy in producing a possible functional role for some of these proteins (see Ref. [50] and previous studies in yeast).


The discovery of an autoimmune response in human and murine JNCL potentially has important implications for pathogenesis. However, it will be crucial to determine whether this autoimmune response contributes directly to disease processes or is secondary to other events. It also remains to be demonstrated whether this response is JNCL specific or is also seen in other forms of NCL.


Developmental disorders


72 These authors describe the development of a total disability score in LINCL patients, similar to their previous work in JNCL. The scoring system combines quantitative measures of motor, visual and verbal functions plus seizure frequency. Importantly, these measures do not depend on a clinical scale, but on a simple assessment system of reliable recordings made by the patients' families.


A considerable body of literature exists examining the effects of adeno-associated viral-mediated gene therapy in a mouse model of mucopolysaccharidosis type VII. The authors describe the significant effects of gene therapy in mucopolysaccharidosis type VII mice using feline immunodeficiency virus-based vectors in reversing spatial learning and memory deficits and pathological changes. Significantly, these effects were found treating adult mice with an established lysosomal disease of the CNS, indicating that the efficacy of this form of therapy is not restricted to neonatal administration.