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Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) and the Eye

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Abstract

Juvenile neuronal ceroid lipofuscinoses (JNCL) or Batten disease is the most common type of NCL in the United States and Europe. This devastating disorder presents with vision failure and progresses to include seizures, motor dysfunction, and dementia. Death usually occurs in the third decade, but some patients die before age twenty. Though the mechanism of visual failure remains poorly understood, recent advances in molecular genetics have improved diagnostic testing and suggested possible therapeutic strategies. The ophthalmologist plays a crucial role in both early diagnosis and documentation of progression of JNCL. We update Batten disease research, particularly as it relates to the eye, and present various theories on the pathophysiology of retinal degeneration.

Keywords

autofluorescence; Batten disease; ceroid; CLN3; neuronal ceroid ipofuscinosis Ceroid; retinal degeneratio

I. Introduction

The ophthalmologist plays a crucial role in the early diagnosis of juvenile neuronal ceroid lipofuscinosis (JNCL). There has been substantial progress in understanding the molecular genetics of JNCL, in the development of new animal models and less invasive diagnostic

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tests, and, most importantly, in a better understanding of JNCL pathogenesis. The ophthalmologist's role is not limited to diagnosis, as an understanding of the pathophysiology of vision loss may shed light on the systemic manifestations of the disease.

A. BACKGROUND

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited lysosomal storage diseases that together constitute the most common neurodegenerative disorders of childhood. They are clinically and genetically heterogeneous and are characterized by intracellular accumulation of autofluorescent material, neurodegeneration, and blindness. The stored material, ceroid, shares a similar composition to lipofuscin and is present in most tissues, including brain and retina.[31, 32, 79, 85] Historically, four major NCL subtypes (infantile, late-infantile, juvenile, and adult) have been delineated based on age of onset and the ultrastructure of the storage material. With the advent of molecular genetics, the NCLs have been further classified into eight genetically distinct forms, independent of age of onset (Table 1). All forms of NCL are recessively inherited, with the exception of an adult variant (Parry type).[65]

JNCL is the most common type of NCL in the United States and Europe.[26] Visual loss is almost invariably the presenting symptom, though even at an early stage slight mental decline may be detected on neuropsychological evaluation.[5, 12, 13, 22, 56, 86, 91] The disease progresses to include seizures, motor deterioration, problems in speech, mental decline, and finally death.[40] Cardiac problems are also common, especially at late stages of the disease.[40] In advanced disease retinal degeneration is widespread, with neuronal depletion and subsequent atrophy and severe gliosis, similar to that found in advanced retinitis pigmentosa (RP).[12, 13, 82, 91]

The pathophysiology of retinal degeneration in JNCL remains poorly understood; however, it appears likely that the primary defect affects different levels of the visual pathway. Retinal degeneration may be caused by accumulation of storage material in the ganglion cell layer, which may be a primary microglial defect[76, 78] or an upstream insult in the dorsal lateral geniculate nucleus (LGNd), leading to optic atrophy and a retrograde retinal degeneration.[96] The JNCL retina illustrated in Fig. 1 demonstrates accumulations of autofluorescent material predominantly in the photoreceptor cell layer, but also in the ganglion cell layer.

Historically, diagnosis required characterization of the autofluorescent storage material by electron microscopy of rectal, conjunctival, or skin biopsies, peripheral blood, or post-mortem tissue. Current genetic techniques applied to a DNA sample from blood or a buccal swab allow the physician to make an accurate diagnosis and to counsel patients and families more quickly and effectively. Details can be obtained through contacting the Batten Disease Diagnostic and Clinical Research Center at http://dbb.urmc.rochester.edu/labs/pearce/bddcrc/index.htm

JNCL was first described by Stengel (1826) and was amplified by Batten (1903), Spielmeyer (1905), Vogt (1909), and Sjogren (1931). As a result the disease has had various eponyms: Vogt-Spielmeyer disease, Spielmeyer-Sjogren disease, Spielmeyer-Vogt-Sjogren disease, and Batten disease. JNCL may affect patients of any ethnic background. Its

incidence has been estimated at 2 to 4 in 100,000 live births in the United States,[23] and may be highest in Scandinavia, with reports as high as 7 per 100,000 live births.[94]

II. Pathogenesis

Neuropathologically, JNCL has two major features: widespread neuronal degeneration--including retinal atrophy and massive loss of brain substance--and accumulation of intracellular lipopigments. The role of the latter in the disease process is still uncertain. Lipopigments stain bright red with PAS and blue with Luxol-fast blue, are autofluorescent, and display enhanced acid phosphatase activity. This autofluorescence is visible mainly in the perikarya of nerve and glial cells and often expands into the cell body. The complete chemical composition of this autofluorescent lipopigment, often termed ceroid, is not known due to its obvious heterogeneity.[85] Immunohistochemistry has shown that a predominant component is the subunit c of mitochondrial ATP synthase.[68, 98]

Reactive gliosis is characteristic of all forms of NCL, but it is unclear whether glial activation precedes or is triggered by neuronal loss. Activation of microglia and astroglia, before neuronal degeneration, has been postulated.[78] Neuroimmune and inflammatory components of the disease are clearly evident. Studies of CLN3-mouse models for JNCL have revealed autoantibodies to many proteins, several of which are known to be expressed in the CNS,[17, 18, 20, 21] and suggest that this may underlie the apparent neuroimmune response.[52, 53]

A. OCULAR HISTOPATHOLOGY

Histopathology of autopsy eyes demonstrate severe retinal degeneration resembling that of advanced RP.[11–13, 33, 82, 91, 93] No eyes with early disease have been studied.

1. Light Microscopy—Light microscopy reveals normal conjunctiva, cornea, iris, angle, ciliary body, and lens.[33, 93] There is near complete loss of photoreceptor cells, outer nuclear layer, and outer plexiform layer. Some of the retinal periphery may be spared.[33] There is marked atrophy of the nerve fiber layer, ganglion cell layer, and optic nerve.[33, 93] Glial fibrosis is pronounced, mostly in the nerve fiber layer, and especially around vessels.[33] The remaining ganglion cells and some inner nuclear layer neurons are engorged with cytoplasmic granules. No granules are seen in remaining photoreceptor cells.[11] In areas there is retinal pigment epithelial atrophy as well as hypertrophy. The remaining retinal pigment epithelium (RPE) contains fewer lipofuscin granules than controls and is devoid of melanin granules.[11, 33, 93] RPE also contains PAS-positive material, confirmed by electron microscopy (EM) to be typical curvilinear inclusions.

2. Electron Microscopy—EM study of the conjunctiva discloses inclusions with multimembranous material and dense granular material in vascular endothelium, pericytes, fibrocytes, and Schwann cells. Inferior oblique muscle contains intracytoplasmic curvilinear inclusions between myofibrils. Iris fibrocytes, ciliary body pericytes, optic nerve head fibrous astrocytes, central and peripheral retinal ganglion cells, other retinal cells, macrophages in the retina, pericytes and endothelial cells of macular blood vessels, and RPE

all contain atypical intracytoplasmic curvilinear or fingerprint inclusions. The corneal epithelial and endothelial cells, as well as the lens, do not contain inclusions.[11, 33]

B. GENETICS

Mutations in CLN3, a gene localized to chromosome 16p12 that encodes a 438-amino-acid protein of unknown function, underlie JNCL.[23] To date over 30 *CLN3* mutations have been reported, the most common (over 80% of cases) being a 1.02-kb deletion leading to skipping of exons 7 and 8 with early truncation of the CLN3 protein (www.ucl.ac.uk/ncl/).[60–62] Studies have implicated CLN3, or its yeast homolog Btn1p, with lysosomal and/or vacuolar pH regulation, arginine transport defects, nitric oxide signaling, BMP synthesis, endocytic pathways, apoptosis, and autophagy.[16, 27, 34, 39, 55, 66, 67, 71–74] Nevertheless, it appears likely that CLN3 is a lysosomal/endosomal protein that is trafficked through the endoplasmic reticulum and Golgi apparatus.[69, 75] The only study addressing CLN3 localization in the retina utilized a peptide antibody raised to a portion of CLN3 in mice. The resulting immunohistochemistry pointed to a mitochondrial localization, predominantly in Müller cells and in neurons in the inner nuclear layer, with only moderate amounts in photoreceptor inner segment mitochondria.[44] However, specificity of this antibody to CLN3 was not demonstrated. It is therefore also likely that CLN3 is indeed lysosomal/endosomal in retinal cell types.

Systematic characterization of CLN3-mice has revealed that murine models, particularly the *Cln3*$^{-/-}$ mouse,[58] recapitulate the human disease. The clinical manifestations of vision loss, deteriorating motor function, and seizures likely result from specific biochemical and molecular disruptions in the neuronal and glial cell populations associated with these functions.[50, 95, 96]

While the function of CLN3 remains elusive, its loss may result in tissue-specific or cell-specific disease manifestations. While the exact sequence of cellular events in JNCL still requires further clarification, the clinical progression of the disease may be measured by the Unified Batten Disease Rating Scale (UBDRS).[57] Neuropsychological examinations have added to our understanding.[4, 5] Integrating these clinical findings with those from the mouse models for JNCL will be crucial in determining the precise pathophysiology.

C. ANIMAL MODELS

Model systems such as yeast, worms, flies and mice are providing invaluable information on the pathogenesis and molecular mechanisms underlying all the NCLs. Mammalian models exist in the form of sheep (CLN6),[15] cow (CLN5),[42] dog (CLN2 and CLN6),[8, 28] and mouse (CTSD, CLN1, CLN2, CLN3, CLN5, CLN6 and CLN8).[14, 19, 30, 36, 38, 45, 47, 48, 51, 54, 58, 77, 88–90] We will focus on mouse models of JNCL (CLN3*)* and summarize those studies that pertain to the visual system.

1. *Cln3* Mice Models and Vision—Four different CLN3-mouse models have been generated.

a. Cln3$^{-/-}$ Loss of Function (LOF) Mouse: In 1999 Mitchison et al developed the first JNCL mouse model, which, being the first, has also been the most studied. Targeted replacement of exons 1-6 of CLN3 with a neo-cassette in reverse orientation in embryonic stem cells generated a null-allele. Accumulation of autofluorescent material, carbohydrate storage material, and apoptotic cell death were detected in these mice.[36, 59] MRI studies have revealed global changes in the brains.[37] These mice do not manifest retinal degeneration, suggesting that the presence of autofluorescent materials alone may not be sufficient to affect retinal function.[87] The optic nerves are affected.[84] A subsequent study of retinorecipient neurons revealed a specific loss of large projection neurons in the LGNd.[96] These observations suggest that optic nerve degeneration and the loss of the LGNd large projection neurons may underlie or contribute to deterioration in retinal function.

b. Cln3$^{\Delta ex7\text{-}8}$ Knock-in Mouse Model: A second mouse model resembles the most common mutation in JNCL, the 1.02kb deletion.[24] In this model a Lox-P flanked PGK neo-cassette was inserted between exons 7 and 8. These mice also recapitulate the ubiquitous presence of autofluorescent storage material. Interestingly, in older mice (10-17 months old), the *Cln3*$^{\Delta ex7\text{-}8}$ knock-in model demonstrates hypopigmentation of retinas and a significant decrease in the number of cone photoreceptors that directly correlates with the level of hypopigmentation.[24]

c. Cln3 Knock-out (Cln3$^{-/-}$) Mouse Model: A third mouse model used a targeting vector to replace most of exon 7 and all of exon 8 of CLN3 with a neo cassette.[47] These mice also show the characteristic autofluorescent storage material in the CNS. Electrophysiologic testing of 12-14-month-old mice showed a significant reduction in the scotopic b-wave, with no difference in the average a-wave amplitude, resulting in a decrease of the b-wave/a-wave ratio. The average photopic ERG in 12-month-old mice was significantly decreased when compared to normal controls. The 24-month-old *Cln3*$^{-/-}$ mice exhibited slower pupillary light reflex responses at threshold light levels. At maximal light levels, a biphasic response was present, with rapid initiation followed by continued slow constriction that persisted after the light stimulus had ended.

Decreased mean photoreceptor cell density and substantial loss of cells within the inner nuclear layer (INL) were present in the retinas of the *Cln3*$^{-/-}$ mice as compared to age-matched controls. Considerable axonal loss, along with decrease in optic nerve cross-sectional area, were present, similar to that seen in the *Cln3*$^{-/-}$ mice.[46]

d. Cln3 Knock-in Reporter Mouse Model: Eliason et al[30] recently reported the generation of a CLN3 knock-in mouse model. The nuclear localized beta-galactosidase and a 3' simian virus 40 polyadenylation sequence, followed by a neomycin coding sequence driven by the thymidine kinase promoter and exons 9 –13, were ligated into the targeting plasmid just downstream of the neomycin cassette. This mouse model identifies the endogenous expression of CLN3 in the different tissues. The authors report clear expression in the retina; however, further studies are required to determine the extent, if any, of the damage produced by loss of the functional protein.

III. Clinical Presentation

A. CLINICAL HISTORY

Vision loss, including night blindness, photophobia, and loss of peripheral and color vision, is the most common presenting symptom of JNCL.[56, 64, 92] The mean age of onset of visual loss has been estimated to be between 6.4-6.6 years,[13, 22] with presentation to an ophthalmologist at 5.5-8.5 years (mean 7.3 years).[22]

Onset of further neurological decline is variable, being from 1 to 9 years from the initial presentation of deteriorating vision.[13, 86] Typically, the disease is characterized by increasing frequency of seizures and a slow decline in cognitive and motor function. JNCL is invariably fatal.[40] MRI of the brain is usually normal under the age of 10 years; however, during the subsequent years, variable cerebral and cerebellar atrophy appears, the thalamus may show abnormally low signal intensity and periventricular white matter may show high signal intensity on T2-weighted images.[82, 99]

B. CLINICAL EXAM

A precipitous decline in vision is a characteristic feature of JNCL with legal blindness diagnosed within 1-2 years of presentation.[12, 13, 22, 82, 91] There are no anterior segment abnormalities described in JNCL.[43, 93]

1. Ocular Motility—Children have been noted to have eccentric viewing or ‘overlooking,’ holding the eyes in a raised position when attempting to fixate.[22, 91] This feature is attributed to relative preservation of the superior peripheral retina with loss of central and inferior visual field, perhaps due to phototoxicity.[35] Rotary nystagmus may be present on all fields of gaze.[43]

2. Retina and Optic Nerve—Fundus examination at presentation may range from normal to a severe pigmentary retinopathy. Early in the disease, subtle granularity of the retinal pigment epithelium in the central macula may be present, although a bull’s eye maculopathy is classically described. Later in the disease, optic nerve atrophy, vascular attenuation, and pigment accumulation in the peripheral retina develops. The rate of progression is extremely rapid in comparison to other retinal degenerations.[12, 13, 22, 29, 33, 43, 56, 86, 91] .

IV. Differential Diagnosis

The differential diagnosis of JNCL should include all diseases that produce bilateral visual loss in childhood, including Stargardt disease, fundus albipunctatus, retinitis punctata albescens, retinitis pigmentosa, drusen, cone or cone-rod dystrophy, chloroquine/hydroxychloroquine maculopathy, and medically-unexplained visual loss. It is important to note that initial, erroneous diagnoses by ophthalmologists have included many of the above.[13, 22]

V.Diagnostic Testing

A. ELECTROPHYSIOLOGIC TESTING

Characteristic EEG findings include large amplitude and slow wave and spike complexes.[22] Electroretinogram (ERG) generally shows profound loss of amplitude at presentation, particularly under scotopic conditions. The loss of b-wave amplitude is greater than the decrease in a-wave amplitude, creating an electronegative configuration.[22, 97] In early cases, when the visual acuity is normal, ERG may show a normal a-wave and a reduced b-wave; however, repeat testing shows rapidly progressive loss of b-wave amplitude.[41] The relative sparing of the a-wave, indicating that the primary lesion of the retina may be in the inner layers, is consistent with the inner retinal localization of gene product CLN3 found in animal models.[44]

B. LABORATORY TESTING

Vacuolated lymphocytes are found in the peripheral blood of all patients with JNCL.[91] In addition, the deposited autofluorescent ceroid material accumulates in many tissue types and has a characteristic ultrastructural appearance when seen with electron microscopy (see Histopathology above).

C. OTHER CLINICAL TESTING

Fluorescein angiography may define pigmentary disturbances more clearly. In vivo autofluorescence levels have been described to be very low.[56] While not truly diagnostic, variable cerebral and cerebellar atrophy may appear, typically after the age of 10. The thalamus may show abnormally low signal intensity, and periventricular white matter may show high signal intensity on T2-weighted images.[6, 7, 82, 99] There may also be evidence of bilateral mild optic nerve and tract atrophy without cortical involvement.[13, 22]

VI. Diagnosis

Advances in genetic and biochemical understanding of JNCL have lead to less invasive and more efficient methods of diagnosis. Before the common disease alleles were identified, diagnosis relied on the presenting clinical features along with histopathologic examination of peripheral blood and tissue biopsied from either the conjunctiva or rectum (see Histopathology above). DNA tests for common disease alleles are now well established, enabling robust carrier and patient diagnosis. Prenatal diagnosis has also been performed using PCR to identify an allele-specific intragenic microsatellite marker in a chorionic villus sample.[63] Over 80% of affected individuals are homozygotes for the 1.02 kb deletion,[62] and nearly all of the remainder are compound heterozygotes for the 1.02 kb deletion and another missense or nonsense disease-causing mutation. A homogeneous PCR nucleobase quenching assay has been developed to detect the 1.02 kb deletion.[81] In this method, DNA isolated from blood samples or patient fibroblasts is probed with a 6-FAM fluorophore, which distinguishes between normal CLN3 and the common deletion of the CLN3 gene. The 6-FAM fluorophore decreases signal when paired to the amplicon by quenching of guanosine residues. Upon denaturation, the fluorescent signal increases and is detectible.[25] This technique offers fast, accurate, and relatively inexpensive determination of the 1.02 kb

mutation. Detection of other, less common mutations requires nucleotide sequencing. The homogenous PCR nucleobase quenching assay technique should be an early step in determining the genotype and diagnosis of patients suspected of having JNCL. Refinement of these techniques has now enabled rapid diagnosis of JNCL, independent of the mutation, using a DNA sample obtained from a buccal swab.

VII. Treatment

Currently, all treatment for JNCL is symptomatic. Psychotic, affective, and schizophreniform features are managed with citalopram, risperidone, olanzapine, or quetiapine.[9] Reports of decreased D1 dopamine transporter density in JNCL by PET, [1, 80] along with similar findings in one of the *Cln3*$^{-/-}$ mouse models,[95] suggest that JNCL patients may have a dysregulation of the dopamine system, offering a rationale for a trial of dopaminergic medications.[3]

Seizures are treated with anticonvulsants, including, but not limited to, valproic acid, carbamazepine, lamotrigine and clonazepam.[1, 2, 3, 83] Regardless of the specific anticonvulsant used, many JNCL patients' seizures are well controlled.

Murine models may point to new treatment strategies. The autoimmune response first reported in the mouse models is recapitulated in humans, which suggests that targeted immunosuppression might have some benefits.[52, 53, 70] Treating *Cln3*$^{-/-}$ mice with a non-competitive AMPA receptor inhibitor ameliorated motor coordination deficits, and these drugs might also have the potential to slow human disease.[49]

A standardized method to evaluate JNCL patients is crucial, particularly as potential new therapies emerge.[10] Marshall et al have developed and tested a multimodal clinical rating instrument, the Unified Batten Disease Rating Scale (UBDRS).[57] This tool will allow for better monitoring of the evolution of the disease and assessment of the effects of therapeutic interventions.

VIII. Genetic Counseling

The risk of a second child being affected in families with one affected child is 25%. Timely recognition of the diagnosis is therefore critical for the genetic counseling. In addition, early detection and definition of the gene and mutations responsible for JNCL may become important as new therapeutic strategies emerge and clinical trials are undertake. Most mutations can be rapidly identified through a simple PCR reaction, and the rest are defined by sequencing DNA obtained from a buccal swab.

IX. Conclusion and Future Directions

No unifying hypothesis presently exists to explain the molecular mechanisms leading to JNCL. It is not known if storage of lipopigment is a cause or effect of disease.

The development of visual failure in JNCL is poorly understood. It is possible that the accumulation of lipofuscin-like pigment contributes to the progression of disease and 'overwhelms' the RPE, whose job it is to renew photoreceptor outer segments. It is also

possible that the accumulations are cytotoxic to neighboring cells. Perhaps the primary site of damage is not in the outer retina, as suggested by the electronegative ERG[97] and the inner retinal localization of gene product CLN3,[44] but rather a primary degeneration of the LGNd and cortical lesions with retrograde degeneration.[96] JNCL may involve neurodegenerative processes similar to those seen in glaucoma patients. In addition, the role of a neuroimmune response needs further definition.

To understand the mechanisms underlying retinal degeneration in JNCL, it is necessary to better characterize retinal changes in the early stages of disease. Research into the composition and time course of appearance of retinal lipofuscin-like accumulations will provide further clues to pathogenesis of vision failure. Much of the research will rely on animal models that should allow characterization of the role played by the CLN3 protein. The use of non-invasive imaging techniques, such as adaptive optics imaging, to assess patients early in the disease course, may clarity the primary site of retinal disease. Further areas of study include the role of the autoimmune response in vision failure and the role of activated microglia in diseased retinas. With help from ophthalmologists, children will be diagnosed earlier, and clues to the pathogenesis of vision failure may be uncovered.

X. Method of Literature Search

The PubMed database was searched from 1950 to 2007 using the search terms “Batten disease and eye”, “Juvenile neuronal ceroid lipofuscinosis and eye”, and “Neuronal ceroid lipofuscinosis and eye”. English abstracts of non-English articles of significant clinical interest were included where relevant. Additional references of clinical relevance were taken from selected articles.

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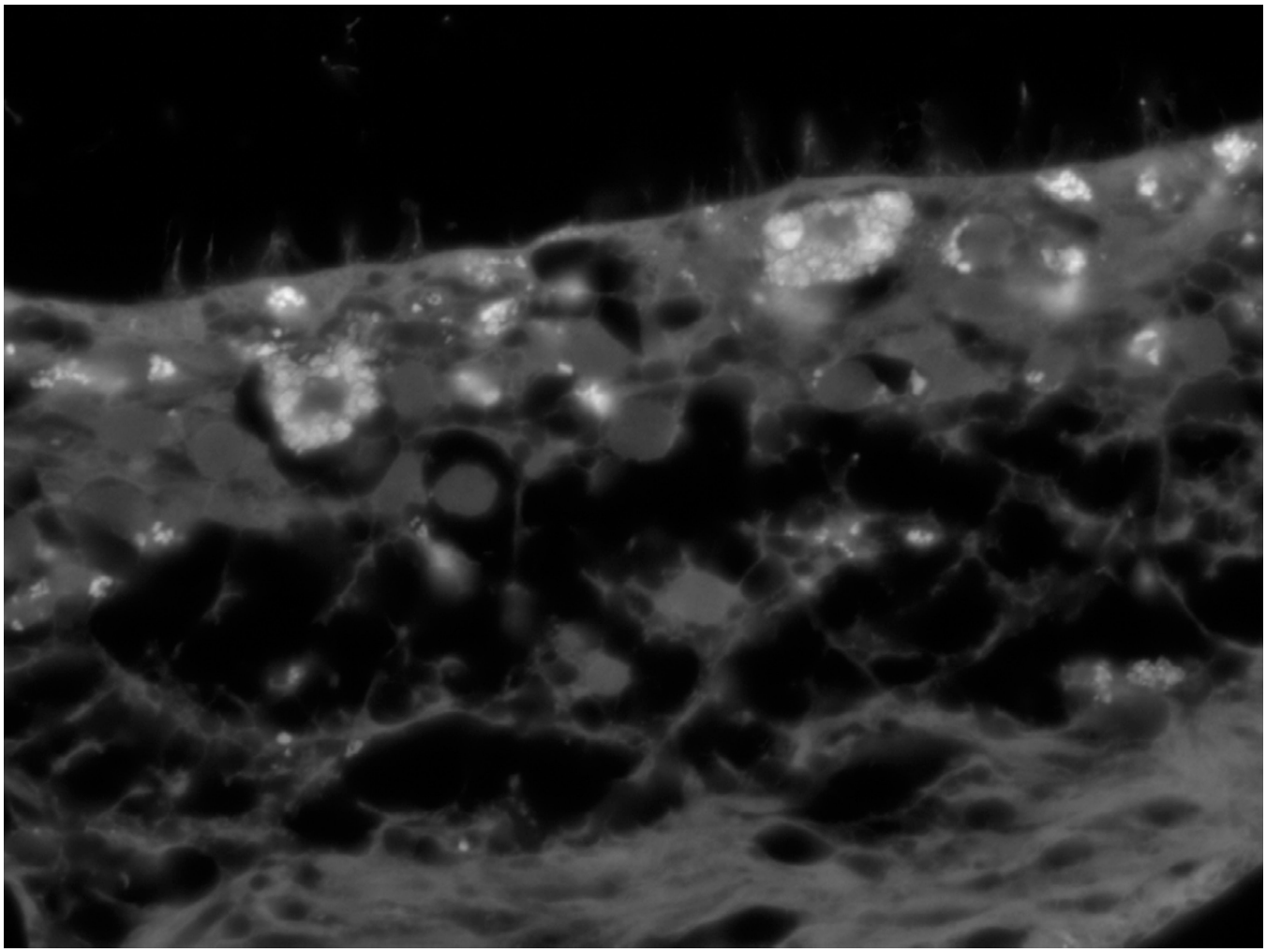

Figure 1.
Autofluorescence in JNCL retina. PR layer is on top, RGC layer bottom. The filter used for the fluorescence is the Zeiss Filter Set 43HE Excitation BP 550/25 Beam Splitter FT 570 Emission BP 605/70.

Table 1

Genes known to cause NCL (adapted from Ramirez-Montealegre D et al. Brain. 2006; 129(6):1353-6).

Disease	Chromosome Location	Gene Affected	Protein
Congenital NCL (CNCL)	11p15.5	*CTSD*	Cathepsin D
Santavuori-Haltia (INCL)	1p32	*CLN1*	Palmitoyl protein thioesterase I
Jansky-Bielschowsky (LINCL)	11p15	*CLN2*	Tripeptidyl peptidase protein I
Batten, Spielmeyer-Sjogren (JNCL)	16p12	*CLN3*	Unknown
Kufs (ANCL)	Unknown	*CLN4**	Unknown
Finnish LINCL (vfinLINCL)	13q31-32	*CLN5*	Unknown
Costa Rican LINCL (vLINCL)	15q21-23	*CLN6*	Unknown
Turkish LINCL (vturkLINCL)	4q28.1-q28.2	*CLN7* (*MFSD8*)	Unknown
Northern Epilepsy/Epilepsy with Progressive Mental Retardation	8p23	*CLN8*	Unknown

INCL (infantile neuronal ceroid lipofuscinoses), LINCL (late infantile neuronal ceroid lipofuscinoses), JNCL (juvenile neuronal ceroid lipofuscinoses), CNCL (congenital neuronal ceroid lipofuscinoses), ANCL (adult neuronal ceroid lipofuscinoses).

* Note : Adult onset NCLs have also been associated to mutations in CLN1.