PUBLICATION HIGHLIGHTS
May-July 2025

Neuronal Ceroid Lipofuscinoses Overview

Malik K, Santucci K, Sremba L, Steenari M, Miele A, Demarest S and Whiteman I.

In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

Summary: This article published by colleagues from Children's Hospital Colorado, Children's Hospital Orange Country and the BDSRA Foundation provides an updated overview of clinical characteristics and genetic causes of all Batten disease (NCL) subtypes. It also discusses clinical evaluation strategies to identify the genetic cause of NCLs, review of management, and approaches to informed counseling of family members of affected individuals.

Same-Day Approach for Combined Intravitreal and Intracerebroventricular Enzyme Replacement Therapy to Prevent Retinal Disease Progression in Children With Neuronal Ceroid Lipofuscinosis Type 2.

Rogers DL, Blind JE, Kienzle T, De Los Reyes E, Mendel TA, Jordan CO.

Pediatr Neurol. 2025 Jun 10;170:1-3. doi: 10.1016/j.pediatrneurol.2025.06.007. Online ahead of print.

Summary: The Nationwide Children's Hospital Batten Center have developed new clinical pathway for same-day administration of both intravitreal (eye) and intracerebroventricular (brain) cerliponase alfa to treat individuals with CLN2 disease, using a preparation technique that takes advantage of the overfill in the vial. This approach aims to slow not only motor decline but also vision loss, offering a more comprehensive treatment option.

Impact of CLN3 Disease on Child Quality of Life and Family Function.

Vermilion J, Augustine EF, Mink JW, McDermott MP, Vierhile A, Pereira-Freitas M, Adams HR.

Pediatr Neurol. 2025 Jun 16;170:17-25. doi: 10.1016/j.pediatrneurol.2025.06.008. Online ahead of print.

Summary: A new study from the University of Rochester Batten Center shows that children with CLN3 disease have significantly reduced quality of life, which worsens as the disease progresses. While families report a substantial overall impact, this does not appear to change in line with symptom severity, highlighting the ongoing need for targeted support for both patients and caregivers.

The Wechsler intelligence scale for children, fourth and fifth editions perform comparably in children with Batten disease.

Adams HR, Augustine EF, Bonifacio K, Collins A, Vierhile AE, Mink JW.

Orphanet J Rare Dis. 2025 Aug 7;20(1):413. doi: 10.1186/s13023-025-03923-w.

Summary: Researchers at the University of Rochester Batten Center found that two versions of a common cognitive test, the WISC-IV and WISC-V, produce comparable results in children and young adults with Batten disease. This means data from both versions can be combined to better understand the cognitive decline associated with the disease over time.

Other Publication Highlights

An AAV variant selected through NHP screens robustly transduces the brain and drives secreted protein expression in NHPs and mice.*

Tecedor L, Chen YH, Leib DE, Ranum PT, Keiser MS, Lewandowski BC, Carrell EM, Lysenko E, Huerta-Ocampo I, Arora S, Cheng C, Liu X, Davidson BL.

Sci Transl Med. 2025 May 14;17(798):eadr2531. doi: 10.1126/scitranslmed.adr2531. Epub 2025 May 14. PMID: 40367194.

* As described in Clinical Program Updates above

Optimized AAV capsids for basal ganglia diseases show robust potency and distribution*

Leib DE, Chen YH, Tecedor L, Ranum PT, Keiser MS, Lewandowski BC, Carrell EM, Arora S, Huerta-Ocampo I, Lai D, Fluta CM, Cheng C, Liu X, Davidson BL.

Nat Commun. 2025 May 19;16(1):4653. doi: 10.1038/s41467-025-60000-3. PMID: 40389462; PMCID: PMC12089535.

* As described in Clinical Program Updates above

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease*

Musunuru K, Grandinette SA, Wang X, Hudson TR, Briseno K, Berry AM, Hacker JL, Hsu A, Silverstein RA, Hille LT, Ogul AN, Robinson-Garvin NA, ... Ahrens-Nicklas RC.

N Engl J Med. 2025 May 15. doi: 10.1056/NEJMoa2504747. Epub ahead of print. PMID: 40373211.

*While this research was carried out in another rare condition (CPS1 deficiency), this personalized base-editing treatment represents an outstanding development in N-of-1 therapies that may have direct applications to the treatment of Batten disease.

We are excited to have Dr Rebecca Ahrens Nicklas as a confirmed keynote speaker at NCL2025 Congress in October. Visit www.ncl2025.org for more details.

PLA2G15 is a BMP hydrolase and its targeting ameliorates lysosomal disease
Nyame K, Xiong J, Alsohybe HN, de Jong APH, Peña IV, de Miguel R, Brummelkamp TR, Hartmann G, Nijman SMB, Raaben M, Simcox JA, Blomen VA, Abu-Remaileh M.

Nature. 2025 May 7. doi: 10.1038/s41586-025-08942-y. Online ahead of print.

Natural history and variants in neuronal ceroid lipofuscinoses: Uncoupling genotype and phenotype.

Mole SE.

Dev Med Child Neurol. 2025 Aug 2. doi: 10.1111/dmcn.16442. Online ahead of print.

Milasen: The Emerging Era of Patient-Customized N-of-1 Antisense Oligonucleotides as Therapeutic Agents for Genetic Diseases.

Wilton-Clark H, Yan E, Yokota T.

Methods Mol Biol. 2025;2964:85-93. doi: 10.1007/978-1-0716-4730-1_4.

Age at onset and gene variants predict lifespan and disease duration in childhood neuronal ceroid lipofuscinoses.

Simonati A, Pezzini F, Nardocci N; CLNet Consortium; Santorelli FM.

Dev Med Child Neurol. 2025 Jul 24. doi: 10.1111/dmcn.16416. Online ahead of print.

Gene therapy ameliorates neuromuscular pathology in CLN3 disease.

Ziółkowska EA, Jablonka-Shariff A, Williams LL, Jansen MJ, Wang SH, Eultgen EM, Wood MD, Hunter DA, Sharma J, Sardiello M, Reese R, Pestronk A, Sands MS, Snyder-Warwick AK, Cooper JD.

Acta Neuropathol Commun. 2025 Jul 23;13(1):160. doi: 10.1186/s40478-025-02059-z.

Autosomal dominant Kufs disease in a Georgian adult woman: A case report.

Papiashvili N, Gagua S, Gonjilashvili N, Okujava N, Tsereteli A.

Epilepsy Behav Rep. 2025 Jul 10;32:100805. doi: 10.1016/j.ebr.2025.100805. eCollection 2025 Dec.

Case Report: The window that closed too soon: lessons from a late CLN2 diagnosis and death of a 9-year-old boy.

Bryzik A, Larysz D, Larysz P, Karpierz JI, Paprocka J.

Front Genet. 2025 Jul 4;16:1622185. doi: 10.3389/fgene.2025.1622185. eCollection 2025.

AAV-delivered PPT1 provides long-term neurological benefits in CLN1 mice and achieves therapeutic levels in sheep brain.

Alam MS, Khatiwada A, Eaton SL, Cohen DM, White J, Derby M, Peterson D, Rivera-Pena G, Nayal M, Becker M, Beck H, Li C, Gentzel R, Atkins G, Greenhalgh SN, Lillico SG, Gregson R, Clutton E, Murdoch F, Nixon J, Gray M, Thompson G, McBride J, Wishart TM, Biferi MG, Ramsburg E.

Mol Ther. 2025 Jul 17:S1525-0016(25)00546-5. doi: 10.1016/j.ymthe.2025.07.011. Online ahead of print.

Downregulation of AKT-mediated $p27^{Kip1}$ phosphorylation with shift to sphingomyelin synthesis in CLN3 disease.

Bilal F, Soueid J, Saab S, Makhoul N, Hamze Z, El-Bazzal L, Makoukji J, Boustany RM.

IBRO Neurosci Rep. 2025 Jun 27;19:223-234. doi: 10.1016/j.ibneur.2025.06.005. eCollection 2025 Dec.

Glucosylsphingosine is a potential fluid-based biomarker of lysosomal dysfunction in $Cln3^{\Delta ex7/8}$ mice.

Wald H, Cicalese S, Yao L, Hatcher N, Luo W, Shen X, Ping X, Culp B, Metzger D, Ault M, Nunes C, Cosden M, Jinn S, Uslaner J, Smith S, Marcus J, Drolet R.

Neurobiol Dis. 2025 Jul 8;214:107026. doi: 10.1016/j.nbd.2025.107026. Online ahead of print.

CLN3 disease disrupts very early postnatal hippocampal maturation.

Singh JB, Burris DM, Bhuyan S, Thurston T, Oschmann A, Jankowski C, Lu W, Rabinowitz JD, Ahrens-Nicklas RC.

Sci Rep. 2025 Jul 8;15(1):24411. doi: 10.1038/s41598-025-02010-1.

Unraveling Neuronal Ceroid Lipofuscinosis: Insights From Two Pediatric Cases in Peripheral India.

Aman N, Panapil AG, Utage P.

J Child Neurol. 2025 Jun 22:8830738251346920. doi: 10.1177/08830738251346920. Online ahead of print.

Benchmarking Nanopore Sequencing for CLN2 (TPP1) Mutation Detection: Integrating Rapid Genomics and Orthogonal Validation for Precision Diagnostics.

Teker B, Akan G, Kazan HH, Özgen Ö, Tatonyan S, Balci MC, Karaca M, Kurekci F, Y ld z EP, Güngor O, Deniz A, Gedikbasi A, Atalar F, Gokcay GF, Poda M.

Int J Mol Sci. 2025 May 23;26(11):5037. doi: 10.3390/ijms26115037.

Mistargeting and ER retention of CLN7 patient-associated nonsense and sequence deletion mutations as a novel cause for CLN7 disease.

Valigi F, Uebler L, Storch S.

Hum Mol Genet. 2025 Jun 9:ddaf089. doi: 10.1093/hmg/ddaf089. Online ahead of print.

Therapeutic antisense oligonucleotide mitigates retinal dysfunction in a pig model of CLN3 Batten disease.

Stratton MP, Centa JL, Swier VJ, Pfeifer WL, Booth CD, Albert K, Hunyara JL, Rechtzigel MJ, Duelli FJ, Leppert HG, Rigo F, Smit T, Jafar-Nejad P, Weimer JM, Drack AV, Hastings ML.

bioRxiv [Note: this is a **Preprint**, not yet peer-review published]. 2025 May 31:2025.05.30.656864. doi: 10.1101/2025.05.30.656864.

Neuronal lipofuscinosis caused by Kufs disease/CLN4 DNAJC5 mutations but not by a CSPα/DNAJC5 deficiency.

López-Begines S, Borjini N, Lavado-Roldán Á, Mesa-Cruz C, Mavillard F, Wiersma VI, Rubio-Pastor F, Tumini E, Paradela-Leal C, Chiclana-Valcárcel ML, Aguado C, Luján R, Scheper W, Nieto-González JL, Fernández-Chacón R.

Sci Adv. 2025 May 23;11(21):eads3393. doi: 10.1126/sciadv.ads3393. Epub 2025 May 21.

Evidence of the impact of CLN2 and CLN3 Batten disease on families in the United Kingdom.

Mole SE, Gissen P, Nordstrom S, Wait S, Allen L, Antonini M, Brownnutt L, Brown R, Cole B, Gibbon F, Henderson RH, Kenrick S, Sisic Z, Thompson B, Nightingale J.

Orphanet J Rare Dis. 2025 May 12;20(1):223. doi: 10.1186/s13023-025-03747-8.

CLN5 deficiency impairs glucose uptake and uncovers PHGDH as a potential biomarker in Batten disease.

Marchese M, Bernardi S, Vivarelli R, Doccini S, Santucci L, Ogi A, Licitra R, Zang J, Soliymani R, Mero S, Neuhauss SC, Ciarmoli L, Signore G, Lalowski MM, Santorelli FM.

Mol Psychiatry. 2025 May 9. doi: 10.1038/s41380-025-03043-8. Online ahead of print.

Niemann Pick C1 mistargeting disrupts lysosomal cholesterol homeostasis contributing to neurodegeneration in a Batten disease model.

Appu AP, Bagh MB, Plavelil N, Mondal A, Sadhukhan T, Singh SP, Perkins NJ, Liu A, Mukherjee AB.

Sci Adv. 2025 May 9;11(19):eadr5703. doi: 10.1126/sciadv.adr5703. Epub 2025 May 7.

UNRAVELING CLN7 disease: the distinct roles of two close MFSD8/CLN7 splice variants in phenotypic expression.

Venier AC, Savy S, Carro G, Guelbert G, Grondona E, Guelbert N, Nicola JP, Pesaola F, De Paul AL.

Hum Mol Genet. 2025 Jun 18;34(13):1157-1167. doi: 10.1093/hmg/ddaf067.

Neuronal ceroid lipofuscinosis type 11 in early childhood.

Singh C, Kiran N, Kampani G, Dhamija K.

BMJ Case Rep. 2025 May 2;18(5):e265803. doi: 10.1136/bcr-2025-265803.

Genetic Reasons for Phenotypic Diversity in Neuronal Ceroid Lipofuscinoses and High-Resolution Imaging as a Marker of Retinal Disease.

Huey J, Gupta P, Wendel B, Liu T, Bharadwaj P, Schwartz H, Kelly JP, Chang I, Chao JR, Sabesan R, Nagiel A, Mustafi D.

Ophthalmol Sci. 2024 May 29;4(6):100560. doi: 10.1016/j.xops.2024.100560. eCollection 2024 Nov-Dec.

Defective anterograde protein-trafficking contributes to endoplasmic reticulum-stress in a CLN1 disease model.

Plavelil N, Appu AP, Gopal KC, Mondal A, Perkins N, Mukherjee AB.

Neurobiol Dis. 2025 Jun 1;209:106890. doi: 10.1016/j.nbd.2025.106890. Epub 2025 Mar 28.

Characterisation of sleep in a mouse model of CLN3 disease revealed sex-specific sleep disturbances.

Kane KM, Iradukunda D, McLouth CJ, Guo LZ, Wang J, Subramoniam A, Huffman D, Donohue KD, O'Hara BF, Sunderam S, Wang QJ.

J Sleep Res. 2025 Aug;34(4):e14461. doi: 10.1111/jsr.14461. Epub 2025 Jan 28.