

Alex TLC Research Summary

September 2026



Research summary of recent leukodystrophy research and clinical trials, includes article summaries and direct links to websites and articles.

Clinical trial updates

[Adrenoleukodystrophy \(ALD\)](#)

Minoryx and Neuraxpharm complete enrolment in leriglitazone pivotal Phase 3 trial (CALYX) in adult patients with cerebral Adrenoleukodystrophy (cALD)

https://www.minoryx.com/media/minoryx_and_neuraxpharm_complete_enrolment_in_leriglitazone_pivotal_phase_3_trial_calyx_in_adult_patients_with_cerebral_adrenoleukodystrophy_cald/

The last patient has been enrolled in the global Phase 3 clinical trial CALYX which is evaluating leriglitazone in adult male patients with cerebral adrenoleukodystrophy (cALD). CALYX is a global, double-blind, randomized placebo-controlled Phase 3 clinical trial in which neither participant nor researcher know who has received the real treatment or placebo. CALYX has enrolled 41 adult male patients with cALD in centres across the US, Europe, South America and India.

[Alexander disease \(AxD\)](#)

ZANVASTRO™ (zilganersen) approved by the FDA as the first and only disease modifying treatment for Alexander disease (AxD) in pediatric and adult patients

<https://ir.ionis.com/news-releases/news-release-details/zanvastrotm-zilganersen-approved-fda-first-and-only-disease>

The U.S. Food and Drug Administration (FDA) has approved ZANVASTRO™ (zilganersen) for people living with Alexander disease in the United States, making it the first approved treatment for this rare leukodystrophy. ZANVASTRO was safe and well tolerated in trials with statistically significant stabilisations of speed of walking and improved gross motor function which is the ability to use large muscle groups (arms, legs, torso) to perform whole body movements such as walking, running, sitting upright. Ionis entered a license agreement with Recordati in June 2026 to bring zilganersen to all countries outside of the U.S., regulatory submissions in Europe and Japan are expected in 2027.

[GM2 gangliosidosis](#) and [Krabbe disease](#)

Polaryx Therapeutics Advances Operational Readiness for SOTERIA Phase 2 Basket Trial

<https://investors.polaryx.com/pr/polaryx-therapeutics-advances-operational-readiness-for-soteria-phase-2-basket-trial>

Polaryx Therapeutics is finishing getting ready for the start of the SOTERIA Phase 2 basket trial which they aim to initiate in the fourth quarter of 2026. SOTERIA is a Phase 2, open-label, single arm trial where all participants receive the same drug. It is designed to evaluate the safety, tolerability, pharmacokinetics (how the body processes a drug) and clinical activity of the lead candidate drug PLX-200 in paediatric patients with CLN2 disease, CLN3 disease, Krabbe disease and Sandhoff disease. They have registered on ClinicalTrials.gov under the study identifier [NCT07740512](https://clinicaltrials.gov/study/NCT07740512) which will provide important information including eligibility and active sites as they become available.

Research summaries

[Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy \(CADASIL\)](#)

Heterogenous microglial reactivity contrasts with stable vascular transcriptional programs in mouse models of Alzheimer's, CADASIL, and Traumatic Brain Injury

<https://www.nature.com/articles/s41467-026-75367-0>

The brain's blood vessels and immune cells play important roles in maintaining brain health, but their contribution to neurological disease is not fully understood. This study investigated how cells in the brain respond to three conditions associated with inflammation and vascular dysfunction (blood vessels and circulation affected): Alzheimer's disease (AD), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and traumatic brain injury (TBI). Researchers used mouse models of these conditions and performed single-cell RNA sequencing (scRNA-seq), a technique that allows scientists to examine gene activity in individual cells. More than 250,000 cells were analysed across different stages of disease, providing a detailed picture of how different brain cell types respond. Transcriptional profiling captures transcriptional cell profiles which provides information about how genetic information is expressed, how proteins are produced, and how cells function. Unexpectedly, the researchers found that most vascular cells (make up the blood and lymphatic vessels), including endothelial cells and vascular smooth muscle cells, showed remarkably stable transcriptional profiles. This was observed even when there was clear disease-related pathology. Although some localised vascular changes occurred following TBI, there was little evidence of widespread changes in gene expression across the brain's vasculature which is the body's network of blood vessels. In contrast, microglia, the brain's immune cells, showed substantial and disease-specific changes in gene expression. Different groups of activated microglia were identified, including disease-associated microglia (DAMs), which expressed genes linked to inflammation and immune responses. Interestingly, microglial responses in late-stage TBI became increasingly similar to those observed in AD. The findings suggest that microglia may be more transcriptionally responsive to neurological damage than vascular cells. The similarities between TBI and AD microglial responses may also help explain why traumatic brain injury can increase susceptibility to later neurodegeneration. Overall, this research provides a valuable molecular resource for understanding how neuroinflammation and the brain's vasculature interact across different neurological diseases.

L-2 Hydroxyglutaric Aciduria (L2HGA)

Clinical and Genetic Analysis of L-2-Hydroxyglutaric Aciduria Caused by a Novel *L2HGDH* Mutation with a Concurrent *RYR1* Variant

<https://www.mdpi.com/2073-4425/17/7/735>

L-2-hydroxyglutaric aciduria (L2HGA) is a rare inherited neurometabolic disorder that primarily affects the brain. It is caused by changes in the *L2HGDH* gene, which provides instructions for an enzyme involved in breaking down L-2-hydroxyglutarate. When this enzyme is not working correctly, L-2-hydroxyglutaric acid accumulates in the body and can damage brain cells over time. People with L2HGA can develop developmental delay, intellectual disability, low muscle tone (hypotonia), seizures, movement difficulties and problems with balance and coordination. This study investigated a patient with a complex combination of neurological and muscle-related symptoms. Clinical assessments included brain magnetic resonance imaging (MRI), biochemical testing and electromyography (evaluates health and function of muscles and nerves), alongside whole-exome sequencing (WES) to search for disease-causing genetic variants. The patient had markedly increased levels of 2-hydroxyglutaric acid in urine, supporting a diagnosis of L2HGA. Genetic analysis identified a previously unreported homozygous *L2HGDH* variant (c.589_590insGGC, p.Q197insG), which was classified as likely pathogenic and provided a genetic explanation for the patient's neurometabolic features. Likely pathogenic means there's strong evidence the variant causes a genetic condition, but not sufficient evidence for it to be classified as pathogenic. The researchers also identified a heterozygous variant (two different versions of a gene) in *RYR1*, a gene associated with inherited muscle disorders. However, this variant was classified as a variant of uncertain significance, meaning there is currently insufficient evidence to determine whether it contributed to the patient's symptoms. It was also noted that it was inherited from the patient's mildly affected father. Overall, this case expands the known genetic spectrum of L2HGA and demonstrates the value of combining biochemical, clinical and genomic testing when diagnosing rare and complex neurological disorders. These findings may also support improved genetic counselling and future research into L2HGA.

Megalencephalic Leukodystrophy with subcortical cysts (MLC)

Van der Knaap Disease Unveiled: A Radiological-Genomic Journey From Seizure to Diagnosis

<https://www.cureus.com/articles/494833#!/#>

This case report describes a rare brain disorder called Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC), also known as Van der Knaap disease. It usually begins in infancy with an enlarged head and slow motor development. However, this case highlights an unusual presentation in a 12-year-old boy who developed seizures much later than expected. Despite striking abnormalities on MRI, he was still able to walk independently, showing a mismatch between severe imaging findings and relatively mild symptoms. MRI scans revealed classic features of MLC: widespread white matter swelling and cysts in the temporal and occipito-parietal regions of the brain, including one unusually large 8-cm cyst. Importantly, key brain structures such as the corpus callosum and internal capsule were preserved, helping distinguish MLC from similar disorders. Diffusion imaging showed vasogenic oedema, meaning fluid buildup rather than cell death. Genetic testing confirmed a pathogenic MLC1 mutation (c.135dup), a known founder mutation in certain Indian communities. A founder mutation is a mutation with high frequency in a group that is or was geographically or culturally isolated. The

report emphasises the importance of combining MRI and genetic testing for accurate diagnosis, early family screening, and informed genetic counselling to reduce recurrence in future generations.

[Mucopolidosis Type IV](#)

Bilateral Corneal Dystrophy Revealing Mucopolidosis Type IV: A Case Report

<https://www.cureus.com/articles/464301#!/>

This case report describes a nine-year-old boy whose severe corneal clouding (loss of transparency in cornea) and visual loss since birth led to the diagnosis of mucopolidosis type IV (MLIV), a very rare inherited lysosomal storage disorder. Although MLIV usually appears in infants with developmental delay and progressive neurological problems, this child's earliest and most visible symptom was bilateral epithelial-stromal corneal dystrophy, a disease affecting the outermost layers of the cornea, causing extreme light sensitivity and near-blindness. Beyond the eye findings, the child had seizures, hypotonia (low muscle tone), psychomotor delay (slowing of movement and thought processing), and facial dysmorphism, suggesting a multisystem disorder. Electrophysiology revealed normal retinal function but abnormal visual pathways, consistent with optic nerve involvement. Genetic testing confirmed a homozygous *MCOLN1* nonsense mutation (*c.169C>T; p.Arg57*), which stops the mucopolipin-1 protein from functioning properly and is known to cause MLIV. The report emphasizes that MLIV should be considered in children with congenital corneal opacity plus developmental delay, even outside the Ashkenazi Jewish population where the disease is more common. Early diagnosis prevents unnecessary corneal transplantation, which is ineffective due to recurrence, and allows families to receive appropriate genetic counselling and supportive multidisciplinary care.

Concise Articles

[Canavan disease](#)

Gene Therapy & Disease Burden Impact

<https://myrtellegtx.com/gene-therapy-disease-burden-impact/>

[GM2 gangliosidosis](#)

Andelyn Biosciences to Implement Curator® Platform to Develop and Manufacture Gene Therapy AAV9-GM2 for Queen's University to Treat GM2 Gangliosidoses

<https://www.andelynbio.com/news-media/andelyn-biosciences-to-develop-and-manufacture-gene-therapy-aav9-gm2-for-queens-university-to-treat-gm2-gangliosidoses>

Please be aware these summaries are produced voluntarily by Biomedical Science students and are their interpretations of the information and findings. This information is reviewed by our Research Analyst Kristina Backlund MSc. The

National Lottery Community Fund and Ionis Pharmaceuticals, Inc have contributed to the funding of the Research Analyst role.

Alex TLC assumes no responsibility or liability for any errors or omissions in the content of these summaries. The information contained in the research summaries is provided on an "as is" basis with no guarantees of completeness, accuracy, usefulness, or timeliness.

If you are unsure of any of the details within the summaries, please refer to the actual articles or contact info@alextlc.org

