Alex TLC Research Summary
November 2025

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

Clinical trial updates

Aicardi-Goutières syndrome (AGS)

ImmuneSensor Therapeutics Receives Orphan Drug and Rare Pediatric Disease Designations from the U.S. FDA for cGAS Inhibitor Drug Candidate, IMSB301, for the Treatment of Aicardi Goutières Syndrome (AGS)

https://www.immunesensor.com/news/112024/

The U.S. Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) for ImmuneSensor Therapeutics drug candidate IMSB301 for Aicardi Goutières Syndrome (AGS) which is currently in an ongoing Phase 1 trial. ODD was introduced to encourage the development of drugs to treat conditions affecting fewer the 200,000 people in the US and offers a number of benefits to the pharmaceutical company as well as potentially allowing for priority review. The Rare Paediatric Disease designation offers similar benefits but is concerned with the development of drugs for diseases affecting a small number of children under the age of 18. This program intends to help with the development of new drugs intended to prevent or treat rare paediatric diseases. These are important steps for the development of this treatment for AGS.

Metachromatic Leukodystrophy (MLD)

Kyowa Kirin and Orchard Therapeutics Announce OTL-200 Granted Orphan Regenerative Medicine Product Designation for Early-onset MLD in Japan

https://ir.orchard-tx.com/news-releases/news-release-details/kyowa-kirin-and-orchard-therapeutics-announce-otl-200-granted

Kyowa Kirin and Orchard Therapeutics announced that Japan's Ministry of Health, Labor and Welfare (MHLW) has granted Orphan Regenerative Medicine Product Designation to OTL-200, a gene therapy for the treatment of pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), and early-symptomatic early juvenile (ESEJ) which are collectively referred to as early-onset metachromatic leukodystrophy (MLD). There are currently no approved therapies for MLD in Japan beyond supportive and end-of-life care. Kyowa Kirin is currently preparing to initiate a clinical trial for OTL-200 in Japan. OTL-200 has also been granted Orphan Drug Designation and Priority Review from the Saudi Food and Drug Authority (SFDA) for the treatment of early-onset MLD. These programs are intended to encourage development of new therapies for rare and ultra-rare diseases by streamlining and expediting the review process.

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Research summaries

Adrenoleukodystrophy (ALD)

Clinical and radiological characteristics of adult-onset X-linked adrenoleukodystrophy: a Chinese cohort study and review of the literature

https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-025-04449-1

Adult-onset X-linked adrenoleukodystrophy (ALD) is a rare inherited condition that affects the brain, spinal cord and adrenal glands. In ALD, the body cannot properly break down very long-chain fatty acids (VLCFAs), which then build up and damage the nervous system. In this article, researchers studied seven Chinese men diagnosed with adult-onset ALD (aged 17-46 years). Two patients were diagnosed with adult cerebral ALD (ACALD) presenting cognitive impairment, behavioural and psychological symptoms. One had adrenomyeloneuropathy (AMN) with progressive leg stiffness and weakness. The remaining four were diagnosed with the spinocerebellar variant, characterised by movement and coordination difficulties. All seven individuals had high levels of VLCFA, and most showed (6/7) symptom-free mild hormonal changes, suggesting subclinical adrenal gland dysfunction. Genetic testing revealed six pathogenic variants, including two newly discovered genetic mutations. This study highlights the variable presentations of adult-onset ALD, though elevated VLCFA appears as a reliable marker of the disease. The study also suggests that ALD screening should be considered in male patients diagnosed with Addison's disease (adrenal failure). Early diagnosis of ALD has important implications in improving care and symptom management.

Hypogonadism in adult males with adrenoleukodystrophy

https://www.sciencedirect.com/science/article/pii/S0003426625007838

This study examines how the rare genetic disorder X-linked adrenoleukodystrophy (ALD) may affect male hormone production, specifically the function of the testes and hormonal control of male characteristics, known as hypogonadism. ALD is caused by mutations in the gene ABCD1, which disrupts the body's ability to break down very-long-chain fatty acids (VLCFAs). These fatty acids accumulate in several organs, including the adrenal glands, nervous system and testes. The researchers focused on adult males with ALD and assessed whether they develop low testosterone or other hormone system abnormalities. They found that men with ALD are at higher risk than the general population for two kinds of hormonal problems: central hypogonadism and compensated primary hypogonadism. This means that while some men may still have normal testosterone levels, their hormone signalling is abnormal, and the testes are working harder than normal. Out of 56 adult males with X-linked ALD, 7 men (13%) had central hypogonadism. Among the subset of adults with normal total testosterone in retrospective testing (49 men), 5 (10%) displayed elevated luteinising hormone but normal testosterone, consistent with compensated primary testicular dysfunction. Erectile dysfunction was reported in 25 of the adult men who had normal testosterone levels, representing 51% of that subgroup. Adolescents and infants showed no evidence of testicular dysfunction, with normal anti-Müllerian hormone and inhibin levels. The findings suggest that hypogonadism in ALD may develop quietly, without obvious symptoms. Since hormone problems in ALD could affect fertility, libido, sexual health and general wellbeing, the researchers recommend that adult males with ALD should be monitored for gonadal/hormonal function as part of their routine care. Early recognition might allow timely hormone replacement or supportive intervention.

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Aicardi-Goutières syndrome (AGS)

Case Report: Heterozygous ADAR c.3019G>A pathogenic variant associated with variable neurological symptoms and incomplete penetrance in a four-generational family
https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1453496/full

This study explored a four-generation family carrying a specific change in the ADAR gene (c.3019G>A) to understand how it affects the immune system and the brain. The ADAR gene normally helps regulate the body's immune response by editing RNA, and when it doesn't function properly, the immune system may become overactive and produce too much type-I interferon, which can harm the nervous system. In this family, two individuals with the mutation developed serious neurological symptoms, such as muscle weakness, difficulty walking, and developmental decline, and both showed high levels of interferon in their blood. However, five other relatives with the same mutation had no symptoms, even though many of them also had elevated interferon activity. This reveals "incomplete penetrance", meaning not everyone with the mutation becomes ill, and "variable expressivity", where symptoms differ widely among those who are affected. In summary, the study shows that this ADAR variant increases the risk of neurological disease but does not guarantee it will occur. Monitoring interferon levels may help identify individuals at risk before symptoms start, and in the future, treatments that target the interferon pathway could help prevent or reduce damage. These findings highlight the importance of combining genetic testing with immune system monitoring to improve early diagnosis and personalised treatment strategies.

Alexander disease (AxD)

Growth Differentiation Factor 15 Elevation in the Central Nervous System Is Associated With Failure to Thrive in Alexander Disease

https://onlinelibrary.wiley.com/doi/10.1002/acn3.70209

Alexander Disease (AxD) is a rare, genetic neurological disorder caused by mutations in the *GFAP* gene. It primarily affects astrocytes and leads to symptoms such as developmental delays, seizures, and a severe problem known as failure to thrive, where affected children struggle to gain weight and maintain muscle and fat. This study explores whether the protein Growth Differentiation Factor 15 (GDF-15) contributes to this failure-to-thrive symptom. The research found that GDF-15 is elevated in the central nervous system of both AxD rats and human patients, particularly in the cerebrospinal fluid, but not in the blood. In the rat model, GDF-15 was produced by astrocytes in the brainstem and activated neurons in the area postrema, a brain region that controls appetite and feeding. High levels of GDF-15 were linked to reduced food intake, muscle loss, and poor weight gain, suggesting that this protein directly contributes to the failure-to-thrive seen in AxD. Importantly, when the researchers reduced GFAP levels using antisense therapy, GDF-15 levels normalised, and weight gain improved in the animal model. This indicates that targeting astrocyte dysfunction, and specifically the GDF-15 pathway, may help address feeding and growth problems in AxD. These findings suggest that GDF-15 could serve as both a biomarker and a therapeutic target in Alexander Disease. Measuring GDF-15 in cerebrospinal fluid may help monitor disease severity, while simultaneously future treatments aimed at reducing its activity could improve nutrition, growth, and overall quality of life for patients with AxD.

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Cockayne Syndrome

Clinical and genetic analysis of ERCC8-Related cockayne syndrome: hepatic dysfunction as a biomarker, anhidrosis as a rare feature, and rehabilitation outcomes for ankle contractures

https://pmc.ncbi.nlm.nih.gov/articles/PMC12364674/

Cockayne Syndrome (CS) is a rare inherited disorder that progressively affects growth and multiple organs, including the brain. CS is often misdiagnosed as clinical manifestations overlap with cerebral palsy (CP). This study, conducted in China, analysed the cases of eight children (6 males, 2 females) with ERCC8 gene-related CS, who were initially misdiagnosed with CP. The aim was to identify features distinguishing CS from CP more clearly. All eight children exhibited early motor delay and Achilles tendon contracture, small head size and growth failure. Brain scans showed white matter loss and brain abnormalities in 6 out of 8 patients. Many had dental problems, abnormal skin reaction to sunlight, and two exhibited anhidrosis (no sweating). Every patient showed high liver enzyme levels, and worse liver function was linked with more severe disease, suggesting that hepatic dysfunction could serve as a biomarker for disease progression. Genetic testing confirmed several pathogenic ERCC8 gene variants resulting from different mutation types (exon deletions, nonsense, frameshift and splice-site mutations). Although no definitive treatments exist, rehabilitation therapy improved mobility and balance. While CS is incompletely understood, this study suggests that genetic testing is essential for definitive diagnosis, liver function assessment is relevant in disease monitoring, and early rehabilitation can improve motor function and quality of life.

Leigh Syndrome

Dysfunctional LHX6 pallido-subthalamic projections mediate epileptic events in a mouse model of Leigh Syndrome

https://www.jci.org/articles/view/187571

Leigh Syndrome (LS) is a rare neurological disorder caused by defects in mitochondria, the cell's energy supplier. Many individuals with LS experience treatment-resistant seizures, but the mechanisms behind this mitochondrial epilepsy remain poorly understood. In this study, researchers used a mouse model lacking a key mitochondrial protein, NDUFS4, which closely mimics human LS. They found that this mitochondrial dysfunction particularly damaged a subset of inhibitory neurons that produce a protein called LHX6 within a brain region known as the external globus pallidus (GPe). The loss of these cells disrupted the balance between excitation and inhibition in brain circuits, ultimately leading to increased seizure susceptibility. Notably, restoring NDUFS4 in the GPe using a gene therapy approach prevented seizures and extended the lifespan of the treated mice. The study also identified the subthalamic nucleus (STN) as an important contributor to the propagation of seizures in the context of mitochondrial dysfunction. When researchers silenced excitatory neurons in the STN, the frequency and severity of seizures were reduced. Together, the findings highlighted the role of the GPe-STN circuit in the development of epilepsy in mitochondrial disorders. Data further suggested that restoring mitochondrial function in the GPe or reducing STN hyperactivity may represent promising novel approaches to tackle mitochondrial epilepsy.

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Mitochondrial Disease

Mitochondrial Donation in a Reproductive Care Pathway for mtDNA Disease

https://www.nejm.org/doi/full/10.1056/NEJMoa2503658

Mitochondrial DNA (mtDNA) diseases are inherited conditions passed from mother to child that can cause severe, sometimes fatal health problems. These diseases occur when the mitochondria do not work properly due to faulty DNA. There are currently very few treatment options, and women with mtDNA mutations face uncertainty about passing the condition on to their children. This study describes how the UK's National Health Service (NHS) created a special reproductive care pathway to help these women make informed choices, including the option of mitochondrial donation. Mitochondrial donation is a technique where the mother's egg, containing her nuclear DNA, is combined with a donor's healthy mitochondria. This allows the child to inherit the mother's genes while avoiding harmful mtDNA. Since 2017, twenty-five women with mtDNA mutations have started or completed this procedure, and eight healthy babies have been born. Tests showed that these babies had no or very low levels of faulty mtDNA. All were born healthy, and their early development has been normal. A few children developed minor health issues, such as hyperlipidemia (high levels of lipids in the blood) or cardiac arrhythmia (an irregular heartbeat), but both of these conditions responded to treatment. The results show that mitochondrial donation can greatly reduce the risk of passing on serious mtDNA diseases and ongoing monitoring will help understand long-term safety. This research provides a safe way to have healthy, genetically related children and offers new hope to families affected by mitochondrial conditions.

POLR3 related leukodystrophy

Critical functional domains in pediatric onset TUBB4A-related leukodystrophy: a clinical and caregiver's perspective

https://www.sciencedirect.com/science/article/abs/pii/S0887899425002875

TUBB4A-related leukodystrophy (TUBB4A-LD) is a rare inherited white matter disorder characterised by progressive developmental and motor dysfunction influenced by genotype and age of onset. This study aimed to better understand how the disease affects families and identify Clinical Outcome Assessments (COAs) to optimise future clinical trial designs. The cohort included 58 caregivers of 58 children with TUBB4A-LD. Participants completed several standardised questionnaires evaluating children's daily skills, motor and communication abilities (VABS-3, PedsQL, HRQOL), and the emotional and physical impact on families (CPCHILD, CareQoL). Results showed that affected children preserve communication and social skills for a longer period than motor skills. To improve their children's quality of life, caregivers prioritised comfort, health and communication. Families also reported high emotional suppression and feelings of loss related to their child's condition. The authors found that CPCHILD and PedsQL tools most effectively captured the challenges faced by patients and caregivers and suggested these measurements could be valuable for assessing treatment outcomes in future clinical trials. Although larger sample sizes are needed to validate these COAs for progressive diseases like TUBB4A-LD, the findings highlight the importance of including caregiver and patient perspectives when developing support programs and clinical trials for TUBB4A-LD.

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

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