

# Unraveling X-linked adrenoleukodystrophy: from genetic roots to therapeutic horizons

## Abstract

X-linked adrenoleukodystrophy (X-ALD) is a severe inherited metabolic disorder caused by mutations in the ABCD1 gene. This review integrates the genetic, biochemical, clinical, and therapeutic aspects of the disease. We describe the role of the ALDP transporter in peroxisomal beta-oxidation and how its dysfunction leads to the accumulation of very-long-chain fatty acids (VLCFAs) and subsequent neurotoxicity. We also highlight advances in newborn screening and modern treatments, such as hematopoietic stem cell transplantation and the newly approved gene therapy (elivaldogene autotemcel), discussing their indications and limits. The objective is to provide a comprehensive update on X-ALD management and future perspectives.

**Keywords:** X-linked adrenoleukodystrophy, ABCD1 gene, very-long-chain fatty acids, newborn screening, gene therapy

Volume 9 Issue 1 - 2026

**Julia Fernandes Freire, Alexandre Azenha Alves de Rezende**

Institute of Exact and Natural Sciences of Pontal, Federal University of Uberlândia, Ituiutaba-MG, Brazil

**Correspondence:** Alexandre Azenha Alves de Rezende, Institute of Exact and Natural Sciences of Pontal, Federal University of Uberlândia, Ituiutaba-MG, Brazil

**Received:** September 30, 2026 | **Published:** October 15, 2026

## Introduction

X-linked adrenoleukodystrophy (X-ALD) is a severe inherited metabolic disorder that affects approximately 1 in 17,000 births, with an incidence comparable to that of phenylketonuria.<sup>1</sup> It is a peroxisomal disorder caused by mutations in the ABCD1 gene, which encodes the adrenoleukodystrophy protein (ALDP), an ATP-binding cassette (ABC) superfamily transporter located in the peroxisomal membrane (Katam et al., 2025).<sup>2</sup>

The disease was initially described as a condition primarily affecting the cerebral white matter and the adrenal cortex; however, X-ALD is currently recognized as exhibiting an extremely heterogeneous clinical spectrum (Manor et al., 2021).<sup>3</sup> Clinical manifestations range from rapidly progressive and fatal childhood cerebral forms, characterized by inflammatory demyelination of the central nervous system, to milder adult forms such as adrenomyeloneuropathy (AMN), which presents as a chronic progressive myelopathy.<sup>2-4</sup>

The clinical importance of X-ALD lies not only in its severity and phenotypic heterogeneity, but also in the fact that more than 70% of affected males develop primary adrenal insufficiency, a potentially fatal condition if not diagnosed and treated appropriately. In addition, approximately 60% of males with X-ALD develop progressive cerebral white matter lesions over their lifetime, and nearly all are at risk of developing myelopathy (Montoro et al., 2021).

Early diagnosis is essential for improving patient prognosis, as it allows for appropriate monitoring, treatment of adrenal insufficiency, and timely therapeutic intervention, such as hematopoietic stem cell transplantation in cases of early-stage cerebral disease (Menezes et al., 2024).<sup>3</sup> In this context, newborn screening for X-ALD has been implemented in several countries, including the United States, with the aim of identifying cases early and preventing severe complications (Manor et al., 2021; Turk, Moser, and Fatemi, 2017).

This article presents a review of the genetic, biochemical, clinical, and therapeutic aspects of X-linked adrenoleukodystrophy, based on recent scientific literature, seeking to bring together information that contributes to an integrated understanding of this metabolic disease.

## Methods

This is a descriptive study, in the form of a narrative and integrative review of the scientific literature, focused on the genetic, biochemical, clinical, and therapeutic aspects of X-linked adrenoleukodystrophy (X-ALD). Documentary and genomic data were gathered from bibliographic databases and biological data platforms, such as PubMed, Scopus, Web of Science, the National Center for Biotechnology Information (NCBI) and the X-ALD mutation database. The literature search covered the period from 1984 to 2026, including articles published in English, Portuguese, and French. Criteria for selecting sources included peer-reviewed original research articles, comprehensive reviews, and clinical guidelines directly related to ABCD1 mutations, VLCFA metabolism, and clinical management of X-ALD. The marker gene ABCD1 was used for genomic analysis. The data analyzed included population incidence, chromosomal localization at Xq28, ABCD1 gene structure, the presence of autosomal pseudogenes on chromosomes 1, 2, 16, 20, and 22, X-linked inheritance patterns, and the diversity of reported pathogenic mutations.

## Genetic Aspects of the ABCD1 Gene

### Chromosomal location and gene structure

The ABCD1 gene (ATP-binding cassette subfamily D member 1) is located on the X chromosome, specifically at Xq28, spans approximately 19.9 kb, and comprises 10 exons as described in the vast majority of the cited literature.<sup>2,3,5</sup> It encodes a 745-amino-acid protein known as the adrenoleukodystrophy protein (ALDP).

ALDP belongs to the ATP-binding cassette (ABC) transporter superfamily, which is characterized by ATP-binding domains that provide the energy for the active transport of substrates across biological membranes.<sup>2,3</sup> The protein is located in the peroxisomal membrane and plays a crucial role in transporting very-long-chain fatty acids (VLCFAs) into peroxisomes, where they are degraded by  $\beta$ -oxidation.<sup>2,3</sup>

Positional cloning studies carried out in 1993 identified the ABCD1 gene and showed that mutations in this gene are responsible for

X-ALD, a milestone in the molecular understanding of the disease.<sup>1</sup> In addition to the functional ABCD1 gene on the X chromosome, there are autosomal ABCD1 pseudogenes located consistently on chromosomes 1, 2, 16, 20, and 22.<sup>3</sup> These pseudogenes are nonfunctional but may interfere with molecular analyses if not properly taken into account.

### X-Linked Inheritance

X-ALD follows an X-linked recessive inheritance pattern, meaning that the mutated gene is located on the X chromosome and the disease manifests predominantly in males, who carry only one copy of the X chromosome (hemizyosity) (Li and Lai, 2022).<sup>6,7</sup> Affected males inherit the mutated allele from their heterozygous carrier mothers, who are usually asymptomatic or show milder clinical manifestations owing to random X chromosome inactivation (Li and Lai, 2022; Taherian et al., 2016).<sup>8</sup> Given the X-linked inheritance pattern, genetic counseling and prenatal diagnosis are essential for pregnancies in carrier women, allowing the prevention of new cases of this severe disease.

### Mutations in the ABCD1 Gene

The ABCD1 gene exhibits remarkable mutational heterogeneity, with more than 1,000 pathogenic variants described in the current X-ALD mutation database snapshots.<sup>2,4,5</sup> A detailed breakdown provided by Kumar et al. (2011) based on older database records identified 431 mutations: 221 missense mutations, 113 frameshift mutations, 53 nonsense mutations, 27 amino acid insertions and deletions, and 17 deletions of one or more exons (Taherian et al., 2016).<sup>5</sup> Studies have identified missense mutations in several exons, with exon 1 being particularly affected, as almost half of the reported mutations are located in this region.<sup>5,2</sup>

### Biochemical Aspects

#### ALDP Protein and Peroxisomal Transporter Function

The adrenoleukodystrophy protein (ALDP) is a 745-amino-acid peroxisomal transmembrane transporter that belongs to the ATP-binding cassette (ABC) transporter superfamily. This protein is located in the peroxisomal membrane and plays a crucial role in the metabolism of very-long-chain fatty acids (VLCFAs) (Kumar et al., 2025).<sup>2,3,5,7</sup>

The primary function of ALDP is to actively transport VLCFAs, or more specifically their acyl-CoA derivatives, from the cytoplasm into the peroxisomes, where  $\beta$ -oxidation and degradation occur.<sup>2,3,7</sup> VLCFAs are saturated fatty acids with carbon chains longer than 22 carbon atoms ( $\geq C22:0$ ), with tetracosanoic acid (C24:0) and hexacosanoic acid (C26:0) being the most clinically relevant.<sup>1,2,9</sup> Pathogenic mutations in ABCD1 may induce defects in the stability of ALDP transmembrane structure and ATPase activity, affecting VLCFA localization to peroxisomes.<sup>2</sup>

#### Accumulation of Very-Long-Chain Fatty Acids

The fundamental biochemical characteristic of X-ALD is the systemic accumulation of saturated very-long-chain fatty acids (VLCFAs), particularly C24:0 and C26:0, in plasma and various tissues, including cerebral white matter, spinal cord, peripheral nerves, adrenal glands, and testes.<sup>1,7-10</sup>

VLCFA accumulation results from two main mechanisms: (1) impaired peroxisomal  $\beta$ -oxidation due to ALDP dysfunction, preventing VLCFA degradation; and (2) increased endogenous VLCFA synthesis in the endoplasmic reticulum by elongase enzymes, particularly ELOVL1.<sup>1,3</sup>

### Mechanisms of neurotoxicity

The mechanisms by which VLCFA accumulation leads to neurotoxicity, demyelination, and neurodegeneration remain incompletely understood, representing an active area of investigation. However, several pathophysiological mechanisms have been identified and characterized (Zuo and Chen, 2024; Turk, Moser, and Fatemi, 2017).<sup>5</sup> Excessive accumulation of VLCFAs in the cytoplasm can cause mitochondrial dysfunction and endoplasmic reticulum stress, eventually leading to cell death.<sup>2</sup>

### Diagnosis and emerging therapeutic strategies

Over the past two decades, advances in molecular genetics, neuroimaging, and cellular therapies have profoundly reshaped the therapeutic options available. A significant limitation of conventional molecular approaches is the potential to miss noncanonical or deep intronic variants. Recent case evidence demonstrates that combined trio whole-exome sequencing with RNA-seq analysis can uncover splice-site variants in ABCD1 that standard panels would overlook (Zheng et al., 2023).

Neuroimaging has become an indispensable component of ALD surveillance. Brain MRI detects white-matter lesions at a presymptomatic stage and enables radiographic staging through the Loes score. International consensus guidelines now recommend regular MRI surveillance for all males with confirmed ABCD1 variants.<sup>11</sup> Newborn screening (NBS) for ALD has fundamentally altered the natural history of cerebral ALD by enabling intervention before neurological damage is established (Vogel et al., 2015; Shimozawa et al., 2021). However, it creates significant demands on healthcare systems to provide timely genetic counseling and monitoring (Zhu et al., 2020).<sup>11</sup>

Autologous hematopoietic stem cell gene therapy represents the most significant recent therapeutic advance in ALD. The therapy received regulatory approval in the United States in 2022, under the name elivaldogene autotemcel (marketed as Skysona). The approach involves harvesting the patient's own cells, correcting the ABCD1 defect ex vivo using a lentiviral vector, and reinfusing the corrected cells. While this strategy avoids the risks of graft-versus-host disease, reports of hematologic malignancies in treated patients have prompted a boxed warning, highlighting the need to carefully weigh these severe risks alongside the clinical benefits (Zhu et al., 2020).<sup>12</sup>

### Conclusion

X-linked adrenoleukodystrophy represents a complex metabolic disorder characterized by ABCD1 gene mutations and VLCFA accumulation. Significant progress has been made in understanding its genetic basis and biochemical impact, shifting the landscape from solely symptomatic care to proactive intervention through newborn screening and presymptomatic MRI surveillance. Therapeutic perspectives for X-ALD now encompass traditional hematopoietic stem cell transplantation and the newly introduced gene therapy for early-stage cerebral disease, providing vital options to alter the disease course. Despite this progress, managing the diverse phenotypes of X-ALD and mitigating the risks associated with novel therapies remain critical challenges. Addressing the complexities of the disease necessitates a multidisciplinary approach. Early detection, vigilant monitoring, and timely intervention are essential to improving prognosis and enhancing the quality of life for patients and their families.

## Acknowledgements

None.

## Conflicts of interest

The author declares there is no conflict of interest.

## References

1. Geillon F, Doriane T, Catherine G, et al. Transporteurs ABC peroxyso-maux et adrénoleucodystrophie liée au chromosome X. *Médecine/Scien-ces*. 2012;28(12):1087–1094.
2. Dong B, Wenshan L, Lili X, et al. Identification of two novel mutations of ABCD1 gene in pedigrees with X-linked adrenoleukodystrophy and review of the literature. *Int J Endocrinol*. 2022;2022:1–13.
3. Mohn A, Nella P, Chiara A, et al. ABCD1 gene mutation in an Italian family with X-linked adrenoleukodystrophy: case series. *Endocrinol, Diabetes & Metab Case Rep*. 2021;2021(1):20–0125.
4. Botelho ECM. Adrenal insufficiency by adrenoleukodystrophy. *Health*. 2020;12(1):1–13.
5. Kumar N, Krishna KT, Veena K, et al. Genomic profiling identifies novel mutations and SNPs in ABCD1 gene: a molecular, biochemical and clinical analysis of X-ALD cases in India. *PLOS ONE*. 2011;6(9):e25094.
6. Alimardani M, Nadia S, Mohammad RA, et al. O-10 ABCD1 gene muta-tion in an Iranian family with X-linked adrenoleukodystrophy and diverse clinical manifestations. *JCEM Case Reports*. 2026;4(Supple 1).
7. Zhang M, Shupeng S, Haoran Z, et al. A novel missense mutation in the ABCD1 gene of a Chinese boy diagnosed with X-linked adrenoleukodys-trophy: case report. *Neurol Sci*. 2019;40(5):1093–1096.
8. Dionne A, Denis B, Alexander McCampbell, et al. Adrenomyeloneuropa-thy: report of a new mutation in a French Canadian female. *Can J Neurol Sci*. 2005;32(2):261–263.
9. Grkovic S, F Soli, A Sangalli, et al. A novel mutation of the ABCD1 gene in Serbian X-adrenoleukodystrophy. *Balkan Journal of Medical Genetics*. 2008;11(1):65–68.
10. Amorosi CA, Helena M, Mariela RM, et al. X-linked adrenoleukodystro-phy: molecular and functional analysis of the ABCD1 gene in Argentin-ean patients. *PLoS One*. 2024;47:112–120.
11. Marc E, Wouter JC van Ballegoij, Eric JM, et al. International Recom-mendations. International recommendations for the diagnosis and ma-nagement of patients with adrenoleukodystrophy: a consensus-based approach. *Neurology*. 2022;99:940–951.
12. Jasmine G, Swathi S. Current Opinion in Endocrinology. An update on the diagnosis and treatment of adrenoleukodystrophy. *Curr Opin in En-docrinol, Diabetes Obes*. 2022;30(1):44–51.