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Multi-omics approach for screening of X-linked adrenoleukodystrophy

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Abstract

X-linked adrenoleukodystrophy (X-ALD) is a single-gene disorder that predominantly affects the cerebral white matter, peripheral nerves, adrenal cortex, and testis. As the most prevalent genetic disorder within the peroxisomal group, X-ALD is characterized by impaired metabolism of very long-chain fatty acids (VLCFAs) resulting from mutations in the ABCD1 gene, located on the Xq28 chromosome. The clinical presentation varies widely, with neurological manifestations ranging from progressive, fatal, inflammatory cerebral leukodystrophy in young boys to non-inflammatory axonal myelopathy and peripheral neuropathy in adult males. Over 70% of affected males experience primary adrenal insufficiency, with females presenting with gonadal dysfunction/primary ovarian insufficiency, loss of hair, and early balding. Molecular evaluation and mutation detection provide the most definitive diagnosis, allowing for the assessment of genetic risk and carrier status. This study aims to investigate the mutational spectrum and biochemical prognosis of X-ALD, providing insights into its pathophysiology and implications for clinical management.

Keywords: X-LINKED ADRENOLEUKODYSTROPHY (X-ALD); ABCD1 GENE; VERY LONG CHAIN FATTY ACIDS (VLCFA'S); Metabolomics; New born screening; Lysophosphatidylcholine (LPC); Peroxisomal disorders

1. Introduction

X-linked adrenoleukodystrophy (X-ALD) is a life-altering genetic disorder characterized by a broad spectrum of clinical manifestations that affect multiple organ systems, primarily impacting the nervous system and adrenal cortex. As the most common peroxisomal disorder, X-ALD results from mutations in the *ABCD1* gene, leading to defective beta-oxidation of very long-chain fatty acids (VLCFAs) and their subsequent accumulation within cells [2], [11]. This biochemical defect underlies the diverse and progressive symptoms observed in patients, ranging from severe neurological impairment in children to more chronic and insidious forms in adults.

The pathophysiology of X-ALD is characterized by the accumulation of VLCFAs, which disrupt cellular functions and trigger inflammatory responses, particularly within the brain [10], [11]. Clinically, X-ALD presents a wide range of neurological and endocrinological challenges, with early-onset cerebral forms posing significant morbidity and mortality risks. Another one, including endocrine manifestations, is primary adrenal insufficiency and hypogonadism, which further complicates the clinical picture, compelling the use of comprehensive management strategies [9], [14].

The range in clinical presentation and progression underscores the importance of early and accurate diagnosis, primarily through molecular genetic testing and biochemical assays. Understanding the mutational landscape of the

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ABCD1 gene and its correlation with clinical phenotypes remains crucial in guiding prognosis and therapeutic interventions [11], [13]. This study aims to elucidate the complex interplay of genetic and biochemical factors in X-ALD, contributing to a more in-depth understanding of its pathogenesis and informing future research and clinical approaches.

2. Genetic Transmission of X-ALD

X-linked adrenoleukodystrophy (X-ALD) is inherited in an X-linked recessive manner, which means the gene responsible for the disorder is located on the X chromosome (Xq28), which is 19.9kb and has 10 exons. The mutations in the ABCD1 gene include missense, nonsense, frameshift, and splice-site variants. These mutations result in the loss of the ALDP protein function. While a small proportion may have a milder mutation, allowing some residual activity of the protein. As a result, the risk of transmitting the defective allele varies between males and females. Female carriers, who possess one normal and one mutated copy of the *ABCD1* gene, have a 50% chance of passing the defective gene to their offspring with each pregnancy. If a carrier mother passes the defective gene to her son, he will develop X-ALD, as males have only one X chromosome, whereas if the gene is passed to a daughter, she will become a carrier like her mother, possessing one mutated and one normal X chromosome.

In some cases, females may not be carriers due to de novo mutations or mosaicism at the level of the gonads. De novo mosaicism explains why some females do not exhibit carrier status despite having offspring affected by X-ALD; some X-ALD females can exhibit symptoms due to skewed X-chromosome inactivation or other genetic factors. The frequency of de novo cases in X-ALD varies between 4.1% and 19% [11]. In addition to this, genetic testing is essential for identifying female heterozygotes because up to 15% of them may have normal VLCFA levels, making biochemical screening insufficient for accurate diagnosis [5].

3. Epidemiological Insights of X-ALD

X-ALD demonstrates a notable worldwide presence, with incidence rates that have been more clearly defined in recent years. Before the implementation of newborn screening programs, estimates of X-ALD incidence relied on newly diagnosed cases in comparison to birth rates. These earlier methods indicated that approximately 1 in 20,000 to 1 in 30,000 males are affected. When both male patients and female heterozygous carriers are considered, some studies report a combined incidence of about 1 in 16,800 [11].

A recent study from North Carolina exemplifies the impact of modern newborn screening. Researchers screened dried blood spot samples from over 52,000 newborns and identified four male infants with X-ALD, three female heterozygous carriers, and one case each of peroxisome biogenesis disorder and Aicardi-Goutières syndrome. The study by Lee et al [4] reported a first-tier assay with a predictive accuracy of 67% and a very low false positive rate (0.0057%). These findings suggest an incidence rate for X-ALD of approximately 1 in 30,000, which is consistent with historical estimates.

The accumulating data on X-ALD incidence and genetic transmission underscores the importance of genetic testing and newborn screening. Early detection and counseling are central to effective management and can significantly benefit affected individuals and their families.

4. X-ALD Phenotypes

4.1. Childhood cerebral adrenoleukodystrophy (CCALD)

It affects roughly 35–40% of males [11] with X-linked ALD, typically manifesting around age seven, though onset can vary by a couple of years. Occasionally, symptoms may first present during adolescence or even well into adulthood; for instance, there is a documented case of adult cerebral ALD (ACALD) emerging at age 57 after central nervous system trauma, which suggests that certain triggers might play a role in disease onset. Early clinical features are frequently subtle and may include behavioral disturbances, declining academic performance, impaired auditory discrimination, and diminished visual acuity. Disease progression, unfortunately, tends to be rapid and severe, with most patients developing dementia, ataxia, sensory deficits, and spastic paraplegia. The prognosis is poor; within approximately three years from the appearance of symptoms, most CCALD patients advance to a vegetative state or succumb to the disease. Magnetic resonance imaging (MRI) commonly reveals demyelination of the periventricular white matter, predominantly affecting the occipital region (in 80% of cases) and, less often, the frontal region (20%), frequently beginning in the corpus callosum. These demyelinating lesions are associated with pronounced neuroinflammation,

evidenced by infiltration of lymphocytes, activation of microglia, and elevated concentrations of pro-inflammatory cytokines such as TNF, interleukins, and chemokines [6],[10]

4.2. Adrenomyeloneuropathy (AMN)

AMN affects about 45% of male X-ALD patients. Symptoms typically begin between the third and fifth decades of life, with an average onset age of 28 ± 9 years [11]. The condition progresses slowly, initially impacting the spinal cord and peripheral nerves. Patients may experience spastic paraparesis, impaired vibration sense, sphincter dysfunction, and impotence. Approximately 70% of AMN patients also present with adrenal insufficiency [9], and around 70% show testicular dysfunction, sometimes without other symptoms [9]. About 55% of AMN patients do not develop cerebral involvement ("pure" AMN), while the remaining 45% may show focal CNS demyelination. A retrospective study found that 18% of AMN patients developed severe cerebral demyelination over 10 years, with slower progression than CCALD [5].

4.3. Addison-Only Phenotype

Primary adrenal insufficiency is present in 70% of individuals with X-ALD. The Addison-only phenotype, without neurological involvement, is seen in approximately 10% of male patients. Symptoms may begin as early as age 2, but typically appear between ages 5 and 10. Clinical signs include hyperpigmentation due to elevated ACTH and other features of adrenal dysfunction. Some individuals later develop AMN in adulthood [11].

4.4. Rare Manifestations

Rare adult presentations include hemiparesis, visual field defects, aphasia, increased intracranial pressure, behavioral disturbances, dementia, ataxia, neurogenic bladder and bowel issues, and isolated impotence. Brainstem and cerebellar involvement resembling olivopontocerebellar atrophy may occur, often with severe cognitive decline [20]. Optic atrophy has also been reported in several cases [20].

5. Biochemical Characterization of X-ALD

X-linked adrenoleukodystrophy (X-ALD) is biochemically defined by elevated plasma and tissue levels of very long-chain fatty acids (VLCFAs), particularly hexacosanoic acid (C26:0) and tetracosanoic acid (C24:0) [11]. These elevated levels are found in all male patients and most female carriers, originating from both dietary intake and endogenous synthesis. The high VLCFA content in the brain, adrenal glands, and testis is believed to contribute to the pathological manifestations in these tissues, making VLCFA reduction a key therapeutic goal [10].

The pathogenesis of X-ALD involves mutations in the *ABCD1* gene, which impair VLCFA metabolism. VLCFAs are normally degraded in peroxisomes through β-oxidation, a process involving four enzymatic steps that shorten the fatty acid chain by two carbon atoms at a time. Before degradation, VLCFAs must be activated to their coenzyme-A thioesters in an ATP-dependent reaction catalyzed by very long-chain acyl-CoA synthetase (VLCS) [1]. In X-ALD, elevated VLCFAs result from reduced β-oxidation and diminished VLCFA synthetase activity [11].

The *ABCD1* gene spans 21 kb on chromosome Xq28 and consists of 10 exons, encoding a 745-amino acid peroxisomal ATP-binding cassette transporter known as adrenoleukodystrophy protein (ALDP) [2]. ALDP is an integral peroxisomal membrane protein, with its ATP-binding domain located on the cytosolic side. Although its exact function remains unclear, it is hypothesized to facilitate the transport of VLCFA or VLCFA-CoA into peroxisomes. This function has been demonstrated in yeast but not yet confirmed in mammalian cells [11].

VLCFA elevation in X-ALD is not solely due to impaired peroxisomal β-oxidation but also enhanced VLCFA elongation, resulting in fatty acids with chains up to 32 carbons [11]. An alternative degradation pathway involves microsomal ω-oxidation followed by peroxisomal or mitochondrial degradation of the resulting dicarboxylic acids [11]. However, dicarboxylic acids have not been detected in fibroblasts from X-ALD patients, suggesting that microsomal ω-oxidation is functional but insufficiently effective [11].

The exact role of VLCFA accumulation in tissue pathology remains unclear. It has been proposed that VLCFAs disrupt membrane structure when incorporated into cell membranes [11]. Recent studies suggest that elevated VLCFAs are highly toxic to brain cells due to mitochondrial dysfunction [11] or impaired oxidative stress homeostasis [11]. The relationship among *ABCD1* mutations, reduced peroxisomal β-oxidation, enhanced VLCFA elongation, microsomal ω-oxidation, and tissue damage remains to be fully elucidated.

6. Metabolomics and X-ALD

6.1. Biomarker Discovery

Metabolomics is a powerful approach for understanding the metabolic changes and pathways associated with various physiological and pathological conditions, including X-linked adrenoleukodystrophy (X-ALD). One of the significant advancements in X-ALD metabolomics is the identification of potential metabolite biomarkers. Researchers focus on metabolites that consistently differentiate individuals with X-ALD from those without the disorder. These biomarkers can facilitate early detection, diagnosis, progression monitoring, and treatment efficacy assessment. C26 lysophosphatidylcholine is a notable biomarker, often elevated in dried blood spots (DBS) of X-ALD patients. Elevated C26 levels result from enzyme abnormalities, including VLCFA accumulation and adrenal insufficiency, and serve as a common marker for adrenal dysfunction [11].

6.2. Identification of Metabolic Signatures

Another approach in biomarker discovery involves analyzing hexacosanoic acid and lignoceric acid in DBS samples using LC-MS/MS for X-ALD detection. This study conducted quantitative analyses of C26 and C24, selected as potential markers for diagnosis. The retention times for C26 and C24 were 1 and 1.5 minutes, respectively. The technique was applied to DBS samples from affected and healthy individuals [11].

6.3. Genetics

X-ALD is caused by mutations in the *ABCD1* gene, located on chromosome Xq28 and consisting of ten exons encoding 745 amino acids [2]. To date, 974 mutations have been identified, with 485 being unique [11]. The phenotypic variability of X-ALD is not solely explained by *ABCD1* mutations, suggesting the involvement of modifier genes and environmental factors [13].

6.4. Genotype–Phenotype Correlation

There is no established correlation between the type of *ABCD1* mutation and the main clinical phenotypes of X-ALD and adrenomyeloneuropathy (AMN). Different forms of X-ALD can occur within the same family, and even monozygotic twins with identical mutations may exhibit varying *ABCD1* gene activity, influencing their phenotypes [11].

7. Diagnosis

Metabolomics is a crucial tool for understanding the metabolic changes and pathways associated with various physiological and pathological conditions, including X-ALD [13]. The research aims to identify specific metabolic profiles, potential biomarkers, and the metabolic disruptions linked to the disorder. X-ALD is marked by elevated levels of very long-chain fatty acids (VLCFAs) in the blood and tissues, particularly hexacosanoic (C26:0) and tetracosanoic (C24:0) acids [11]. These elevated levels are found in all male patients and most female carriers, arising from both dietary sources and internal production. The accumulation of VLCFAs in the brain, adrenal glands, and testes is believed to contribute significantly to the disease's symptoms, making VLCFA reduction a key therapeutic target [10].

However, the mechanisms by which *ABCD1* mutations lead to VLCFA accumulation and their degradation via the peroxisomal β-oxidation pathway remain unclear [11]. A novel approach for diagnosing X-ALD involves using LC-MS/MS to analyze hexacosanoic acid (C26) and lignoceric acid (C24) in dried blood spot (DBS) samples. This study quantitatively analyzed these acids as potential markers, with retention times of 1 minute for C26 and 1.5 minutes for C24, applying the method to DBS samples from affected individuals and healthy controls [11].

X-ALD is caused by defects in the *ABCD1* gene on chromosome Xq28 [2], which consists of ten exons encoding 745 amino acids. To date, 974 mutations have been identified, with 485 being unique [11]. The variability in X-ALD symptoms cannot be fully explained by *ABCD1* mutations alone, indicating that modifier genes and environmental factors may also contribute [13]. There is no direct correlation between mutation types and the primary clinical phenotypes of X-ALD and AMN [11]. Different forms of X-ALD can occur within the same family, and even identical twins with the same mutations may display different phenotypes due to variations in *ABCD1* gene activity [11].

Early detection of X-ALD is crucial for timely treatment and improved disease management. Diagnosing the condition before severe symptoms arise can slow or prevent neurological damage, enabling genetic counseling and informed family planning for at-risk individuals [14].

8. Conclusion

This study involved the analysis of samples collected from 14 patients diagnosed with X-linked adrenoleukodystrophy (X-ALD) and an equal number of healthy controls. The patients, aged between 1 month and 16 years, were referred to the Pediatrics and Genetic Lab at Maulana Azad Medical College (MAMC) and Lok Nayak Hospital in New Delhi between June 2023 and April 2024. Urine samples and dried blood spots (DBS) were meticulously collected under sterile conditions to prevent contamination, ensuring the integrity of the samples for subsequent analyses.

Our results demonstrated that the levels of VLCFA metabolites—specifically C20:0, C22:0, C24:0, and C26:0 lysophosphatidylcholine (LPC)—and their ratios were significantly elevated in X-ALD patients compared to healthy controls ($p < 0.05$). The C24:0/C22:0 ratio was notably higher among the patients, while no significant difference was observed in the other VLCFA metabolites except for this ratio. Diagnostic performance evaluated using ROC curves indicated that C24:0 LPC and C26:0 LPC are effective biomarkers for X-ALD at cut-off values of 0.907 μmol/3.2 mm punch and 0.604 μmol/3.2 mm punch, respectively [11].

Genetic sequencing of the *ABCD1* gene revealed pathogenic mutations in 4 patients. Two patients (14.3%) carried missense mutations in Exon 1, one patient (7.1%) had a frameshift mutation in Exon 1 leading to a truncated protein, and one patient (7.1%) exhibited a splice site mutation between Exons 3 and 4. Mothers of the affected individuals were identified as heterozygous carriers, confirming the X-linked inheritance pattern [2], [11].

Clinically, patients presented with a range of neurological and systemic symptoms: 61.5% experienced vision loss, 61.5% reported muscle weakness, 30.8% had hearing deficits, 30.8% showed regression of developmental milestones, and 23.1% presented with behavioral abnormalities. Radiological assessments consistently revealed white matter demyelination in the parieto-occipital regions and changes in the splenium of the corpus callosum. Additional neuroimaging findings included involvement of the frontopontine corticospinal tracts, brainstem, optic radiations, and significant loss of brain parenchyma [6], [10].

These findings underscore the critical importance of VLCFA metabolite profiling and genetic testing for early diagnosis and management of X-ALD. Early identification enables timely interventions and genetic counseling for families, potentially improving clinical outcomes. Further research with larger cohorts is warranted to explore therapeutic targets, such as oxidative stress pathways, and to develop effective treatments [13], [14].

8.1. Treatment and Management

Current treatment options for X-ALD include dietary restrictions to reduce VLCFA intake [19], the use of Lorenzo's oil to decrease VLCFA levels [11], and hematopoietic stem cell transplantation to slow disease progression, particularly when initiated early [19]. Gene therapy presents a promising approach by correcting the defective gene in a patient's stem cells and reintroducing them. The treatment, elivaldogene autotemcel (Skysona), has shown success in halting brain complications and improving outcomes without the risks associated with traditional stem cell transplants [21].

Emerging treatments include troglitazone, currently in phase 3 clinical trials, which seeks to stabilize disease progression in cerebral X-ALD patients. VK00214, another potential therapy, has shown promising results in reducing VLCFA levels in early trials [21]. These advancements offer hope for more effective and less invasive treatments.

Supportive care focuses on enhancing quality of life and alleviating symptoms. This includes regular monitoring of adrenal function and hormone replacement therapy for adrenal insufficiency [10]. Physical therapy improves mobility and manages spasticity, while occupational therapy and adaptive equipment assist with daily activities. Psychological support, such as counseling and support groups, addresses the emotional impact of the disease. Additionally, treatments specific to symptoms—such as seizure control or pain management—are essential for comprehensive care [10].

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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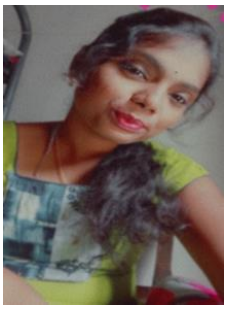
Authors short biography



Sailusha Katam, M.Sc. Sailusha Katam holds a Master's degree in Human Genetics from Andhra University, India, with a strong foundation in molecular biology, genomics, and rare disease research. Her expertise spans multi-omics approaches, including LC-MS, GC-MS, and sequencing technologies, applied to the diagnosis and characterization of rare genetic disorders. She has a keen interest in translational genomics and is actively exploring PhD opportunities in Scandinavian countries to further her research in human genetics. Sailusha is committed to ethical publishing practices and excels in scientific writing, citation formatting, and data integration. Her current work focuses on the mutational spectrum and biochemical profiling of X-linked adrenoleukodystrophy (X-ALD), aiming to improve diagnostic precision and clinical outcomes.