

# PRIMARY LIPID MYOPATHIES: A NARRATIVE REVIEW

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**ABSTRACT** – Primary lipid myopathies (PLMs) are a heterogeneous group of rare, inherited neuromuscular disorders caused by defects in fatty acid transport, mitochondrial  $\beta$ -oxidation, or lipid droplet metabolism. These genetic abnormalities disrupt energy production in muscle cells, leading to clinical manifestations that range from exercise intolerance and recurrent rhabdomyolysis to cardiomyopathy and multisystem involvement.

This narrative review provides a comprehensive overview of the pathophysiological mechanisms, genetic classifications, clinical features, diagnostic strategies, and current treatment approaches for PLMs. Disorders are categorized by the metabolic pathway and subcellular compartment affected: (i) primary carnitine deficiency, (ii) cytoplasmic enzyme or transporter defects [e.g., neutral lipid storage disease (NLSD), *Lipin 1 gene*- (*LPIN1*), Carnitine-Acylcarnitine Translocase (CACT)-related], and (iii) mitochondrial fatty acid oxidation disorders [e.g., Carnitine Palmitoyl Transferase II (CPT II), Very-Long-Chain Acyl-CoA Dehydrogenase (VLCAD), Multiple Acyl-CoA Dehydrogenase deficiency (MADD)]. Clinical presentations are highly variable and may be triggered by metabolic stress, fasting, or exertion.

Diagnosis requires the integration of biochemical assays, muscle imaging, histopathology, and genetic testing, with tandem mass spectrometry and next-generation sequencing playing pivotal roles. Timely recognition is essential, as early dietary and pharmacologic interventions, including carnitine or riboflavin supplementation, can prevent irreversible complications.

While treatment remains largely supportive, emerging therapeutic avenues such as gene therapy and enzyme replacement strategies hold promise. Increased clinician awareness, multidisciplinary management, and future advancements in molecular diagnostics and personalized medicine are essential to improve outcomes for individuals affected by these rare disorders.

**KEYWORDS:** Primary lipid myopathy, Genetics, Diagnostics, Treatment.

**ABBREVIATIONS:** ACADL: Acyl-CoA Dehydrogenase Long Chain; ACADM: Acyl-CoA Dehydrogenase Medium Chain; ACADS: Acyl-CoA Dehydrogenase Short Chain; ACADVL: Very-Long-Chain Acyl-CoA Dehydrogenase; ACAD9: Acyl-CoA Dehydrogenase 9; CACT: Carnitine-Acylcarnitine Translocase; CK: Creatine Kinase; CPT I: Carnitine Palmitoyl Transferase I; CPT II: Carnitine Palmitoyl Transferase II; ETF: Electron Transfer Flavoprotein; ETFA/ETFB: Genes encoding ETF alpha and beta subunits; ETFDH: Electron Transfer Flavoprotein Dehydrogenase gene; ETFQO: ETF-Ubiquinone Oxidoreductase; FA: Fatty Acids; FAO: Fatty Acid Oxidation; HADHA: Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Alpha; HADHB: Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Beta; HADH/HADHSC: Gene coding for Short-Chain L-3-Hydroxyacyl-CoA Dehydrogenase; LD: Lipid Droplets; LCAD: Long-Chain Acyl-CoA Dehydrogenase; LCHAD: Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase; LM: Lipid Myopathies; LPIN1: Lipin 1 Gene; MADD: Multiple Acyl-CoA Dehydrogenase Deficiency; MCAD: Medium-Chain Acyl-CoA Dehydrogenase; MRI: Magnetic Resonance Imaging;

MTP: Mitochondrial Trifunctional Protein; NLSL: Neutral Lipid Storage Disease; NLSL-I: Neutral Lipid Storage Disease Type I; NLSL-M: Neutral Lipid Storage Disease Type M; OCTN2: Organic Cation/Carnitine Transporter 2; PCD: Primary Carnitine Deficiency; PPAR: Peroxisome Proliferator-Activated Receptor; RRF: Ragged Red Fibers; SLC22A5: Solute Carrier Family 22 Member 5 (gene encoding OCTN2); SLC25A20: Solute Carrier Family 25 Member 20 (gene encoding CACT); SCAD: Short-Chain Acyl-CoA Dehydrogenase; SCHAD: Short-Chain L-3-Hydroxyacyl-CoA Dehydrogenase; TMS/MS: Tandem Mass Spectrometry; TG: Triglycerides; VLCAD: Very-Long-Chain Acyl-CoA Dehydrogenase.

## INTRODUCTION

Lipid myopathies (LMs) are rare, multisystem muscle disorders most commonly associated with enzyme defects in lipid metabolism within muscle cells, leading to impaired muscle function. Primary lipid myopathies are caused by genetic mutations, whereas secondary lipid myopathies are acquired forms of the disorder resulting from lifestyle factors, such as an unbalanced diet, or other medical conditions that affect lipid levels<sup>1</sup>.

Although some primary lipid storage myopathies can now be effectively managed, successful outcomes often rely on early and accurate diagnosis; without timely intervention, these conditions can be fatal<sup>2</sup>. However, delayed diagnosis remains common, as many patients are asymptomatic except during periods of fasting or prolonged exercise, and altered biochemical exams can be incidentally detected on routine clinical investigations<sup>3</sup>.

Given the critical importance of early recognition for proper diagnosis and timely treatment, this narrative review aims to provide a comprehensive overview of the genetics and pathophysiological mechanisms underlying muscle dysfunction, diagnostic approaches, and current treatment strategies for primary lipid myopathies, in order to prompt clinicians to consider these diseases in the differential diagnosis process.

The literature search was conducted on PubMed using the following keywords and combinations: "Primary Lipid Myopathy, Genetics, Classification, Diagnosis, Therapy, Treatment, Pathophysiology, and Mechanisms". Primarily, studies on humans published in English within the last 20 years were considered. All types of study designs were included to broaden the scope of this narrative review. Articles were screened, based on full text or abstract, according to their relevance to the topic, as judged by the authors. For each selected study, specific information deemed relevant to the analysis was extracted, with a focus on genetics, pathophysiology, clinical features, diagnostic approaches, and treatments in the context of primary lipid myopathies.

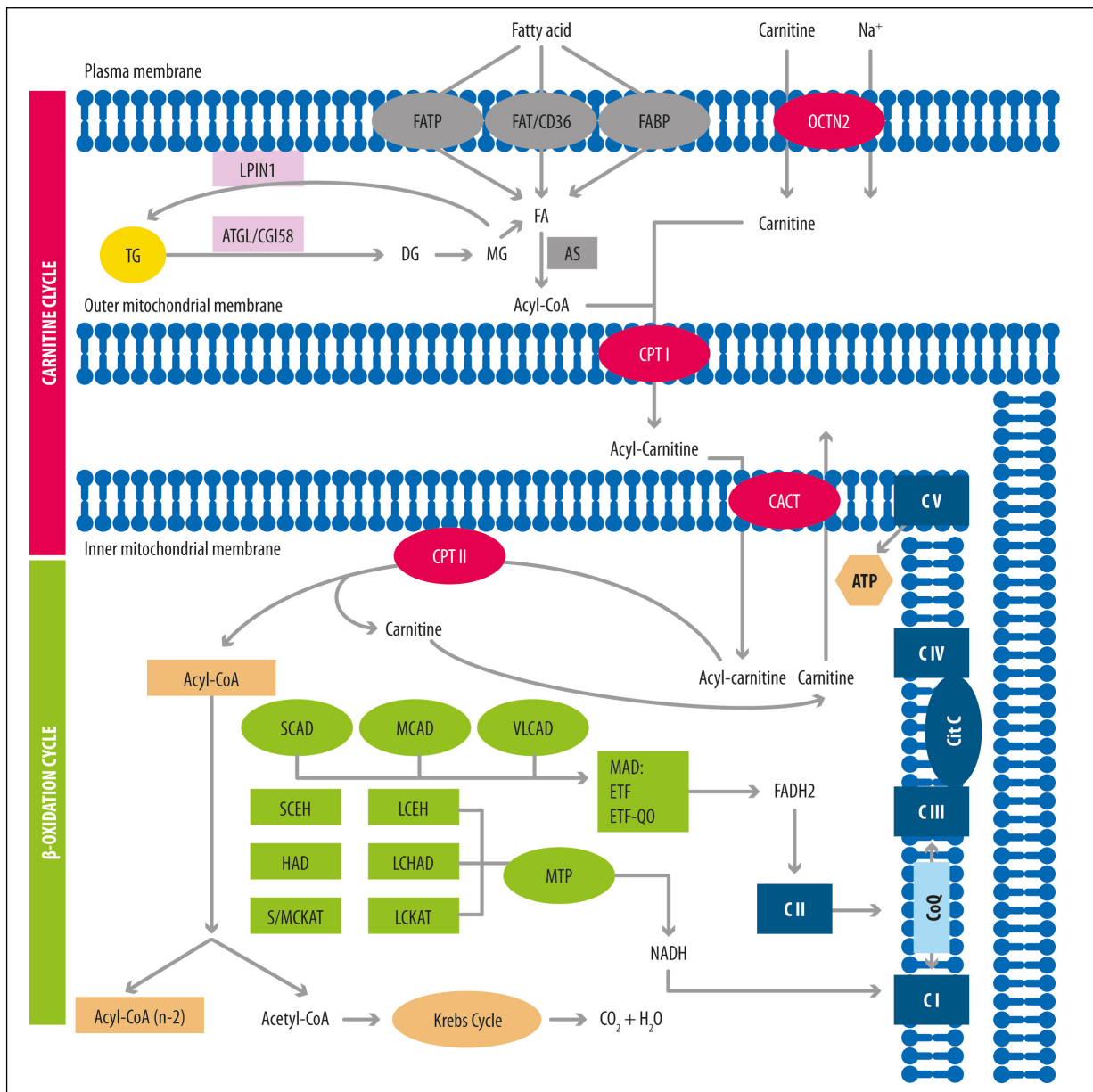
## PATHOPHYSIOLOGICAL MECHANISMS

Fatty acids, composed of long chains of carbon and hydrogen atoms, are the fundamental components of lipids. In muscle fibers, they are metabolized through the fatty acid oxidation (FAO) process to generate energy, particularly during prolonged exercise or fasting<sup>4</sup>. FAO primarily occurs in mitochondria and is known as  $\beta$ -oxidation because it involves the stepwise removal of two carbon atoms from the fatty acid chain at the  $\beta$  (second) carbon position.

The FAO cycle involves several sequential steps (Figure 1). It begins with lipolysis, the breakdown of triglycerides stored in lipid droplets into glycerol and free fatty acids. The fatty acids are then activated in the cytoplasm by binding to coenzyme A to form acyl-CoA. This compound is transported into the mitochondrial matrix *via* the carnitine shuttle, a transport system that facilitates the movement of long-chain fatty acids across the plasma and mitochondrial membranes. Inside the mitochondria, acyl-CoA undergoes  $\beta$ -oxidation to produce acetyl-CoA, which enters the citric acid cycle to contribute to ATP production.

Genetic mutations affecting any of the enzymes or structural proteins involved in these processes can impair lipid breakdown and utilization, leading to muscle dysfunction. The pathogenesis of lipid myopathies arises from both the accumulation of lipid droplets within muscle fibers and the resulting energy deficit, especially in type I (slow-twitch) fibers, which depend primarily on oxidative, glycolysis-independent metabolism. Since skeletal muscle is one of the most energy-demanding tissues, lipid myopathies typically manifest as chronic hypotonia, muscle weakness, and exercise intolerance<sup>6</sup>.

Other high-energy-demand organs, such as the heart, liver, and brain, also rely heavily on mitochondrial oxidative phosphorylation and are therefore vulnerable to disruptions in this metabolic pathway<sup>7</sup>.



**Figure 1.** Main stages in the carnitine and fatty acid  $\beta$ -oxidation cycle. Uptake and activation of FA, in gray: AS: acyl-CoA synthetase; FAT/CD36, FATP: fatty acid transporters. Cycling of carnitine to pass the FA to the mitochondrial matrix, in red: CACT: carnitine-acylcarnitine translocase; CPT I: carnitine palmitoyltransferase I; CPT II: carnitine palmitoyltransferase II; OCTN2: carnitine transporter.  $\beta$ -Oxidation spiral, in green: HAD (M/SCHAD): 3-hydroxyacyl-CoA dehydrogenase; LCHAD: long-chain 3-hydroxyacyl-CoA dehydrogenase; LCEH: long-chain enoyl-CoA hydratase; LCKAT: long-chain 3-ketoacyl-CoA thiolase; MAD: multiple acyl-CoA dehydrogenase; MCAD: medium-chain acyl-CoA dehydrogenase; MTP: mitochondrial trifunctional protein; S/MCKAT: short/medium-chain 3-ketoacyl-CoA thiolase; SCAD: short-chain acyl-CoA dehydrogenase; SCEH: short-chain enoyl-CoA hydratase; VLCAD: very long-chain acyl-CoA dehydrogenase. Electron transfer and respiratory chain pathway, in blue: CI, CII, CIII, CIV, CV: mitochondrial respiratory complexes I, II, III, IV and V; CoQ: coenzyme Q. Source: Ruiz-Sala and Peña-Quintana<sup>5</sup> 2021. Reproduced from MDPI, Basel, Switzerland, under a Creative Commons Attribution (CC BY) (<https://creativecommons.org/licenses/by/4.0/>) licence.

Beyond energy production, lipids are also critical for maintaining cell membrane structure and function, as well as for cell signaling. Because lipid metabolism is closely integrated with immune function, disruptions in lipid pathways can affect immune regulation and cellular homeostasis, contributing to endoplasmic reticulum stress response, inflammation, oxidative damage, and ultimately cell death<sup>8,9</sup>.

Based on the specific phase of lipid metabolism that is impaired, lipid myopathies can be classified into three main groups:

- Disorders causing primary carnitine deficiency;
- Those involving enzymes and proteins active in the cytoplasm;
- Those involving enzymes and proteins functioning within the mitochondria.

Some disorders in the latter two groups may also lead to secondary carnitine deficiency<sup>1</sup>.

## GENETIC CLASSIFICATION AND CLINICAL FEATURES

The spectrum of LM is expanding with the identification of new molecules involved in fatty acid (FA) metabolism, and a definitive classification is still under development<sup>1</sup>. Primary LMs can be categorized according to the main metabolic pathway affected and the intracellular location of the defect, as summarized in Table 1.

The onset of LM can occur at any age, from infancy to late adulthood, and presents with a wide variety of clinical manifestations. Common features include fatigue, exercise intolerance, stable or progressive muscle weakness, or episodic weakness with rhabdomyolysis crises, often triggered by metabolic stressors, such as fever or physical exertion. Muscle atrophy is uncommon, while other organs, including the liver, heart and central nervous system, may also be affected<sup>1</sup>.

### Primary Carnitine Deficiency

Included in some countries as part of the newborn screening programs<sup>10</sup>, primary carnitine deficiency (PCD; OMIM #212140)<sup>11</sup> is caused by homozygous or compound heterozygous mutations in the *solute carrier family 22 member 5 (SLC22A5)* gene, which encodes organic cation/carnitine transporter 2 (OCTN2). OCTN2 is a physiologically important, sodium-dependent, high-affinity carnitine transporter. The estimated prevalence is 1/20,000 and 1/70,000 newborns in Europe and the USA, respectively<sup>12</sup>. The condition is characterized by markedly reduced plasma and tissue carnitine concentrations<sup>13</sup>.

PCD can present with a wide spectrum of clinical manifestations, depending on the age of onset and the residual activity of the OCTN2 transporter. Symptoms range from metabolic crises in infancy, such as hypoketotic hypoglycemia, hyperammonemia, lethargy, or even coma, and steatotic hepatomegaly to progressive dilated cardiomyopathy during childhood, and proximal muscle weakness, severe fatigue, and exercise intolerance in adulthood<sup>2</sup>.

### LM Due to Impaired Enzymes/Proteins Acting Inside the Cytoplasm

This group includes three forms caused by mutations in genes involved in lipid droplet metabolism (*PNPLA2*, *CGI58*, *LPIN1*) and one form associated with a defective transporter responsible for carnitine transfer across the inner mitochondrial membrane (*SLC25A20*).

*PNPLA2* encodes adipose triglyceride lipase (ATGL), while *CGI58* (also known as *ABHD5*) encodes its coactivator. Both enzymes are essential for the catabolism of triglycerides to diglycerides, and their deficiency results in neutral lipid storage disease (NLSD), characterized by non-lysosomal accumulation of neutral lipids in multiple tissues (OMIM #609059 and #604780, respectively)<sup>14-16</sup>. These two genes are associated with two phenotypes that share some overlapping features, and both follow an autosomal recessive inheritance pattern:

- NLSD with myopathy (NLSD-M)
- NLSD with ichthyosis (NLSD-I), also known as Chanarin–Dorfman syndrome.

NLSD-M typically presents with proximal and axial muscle weakness, which may progress to severe disability, along with exercise intolerance, myalgia and fatigue, with a variable age of onset (commonly between the 20s and 40s). Upper limbs are more frequently involved than lower ones, usually asymmetrically. In an Italian cohort study<sup>16</sup>, it was reported that approximately one in four patients had lost their ability to walk independently and required a device after an average follow-up period of 30 years. No respiratory or bulbar muscle involvement was described at follow-up. Dilated or hypertrophic cardiomyopathy may develop in 40-50% of cases, potentially leading to severe heart failure<sup>17</sup>.

**Table 1.** Genetics and classification of primary lipid myopathies.

Disease	Gene	Protein	Main Features
<b>I. Disorders causing primary carnitine deficiency</b>			
PCD	<i>SLC22A5</i>	OCTN2	Low plasma and tissue carnitine levels
<b>II. Disorders involving cytoplasmic enzymes or transporters</b>			
NLSD-M	<i>PNPLA2</i>	ATGL	Accumulation of neutral lipids in tissues. Progressive muscle weakness, cardiomyopathy, lipid accumulation in tissues
NLSD-I	<i>ABHD5 (CGI-58)</i>	CGI-58 (ATGL coactivator)	Accumulation of neutral lipids in tissues. Ichthyosis, mild myopathy, systemic involvement (e.g., liver, CNS, retina)
Lipin-1 deficiency	<i>LPIN1</i>	Lipin-1	Defective lipid metabolism; cytosolic phosphatase and nuclear transcriptional regulator
CACT deficiency	<i>SLC25A20</i>	CACT	Impaired mitochondrial import of long-chain fatty acids
<b>III. Disorders involving mitochondrial FAO</b>			
CPT II deficiency	<i>CPT2</i>	CPT II	Disrupted FA transport into mitochondria
VLCAD deficiency	<i>ACADVL</i>	VLCAD	Impaired $\beta$ -oxidation of long-chain FA
LCAD deficiency	<i>ACADL</i>	LCAD	Similar to VLCAD; long-chain FAO defect
MCAD deficiency	<i>ACADM</i>	MCAD	Most frequent FAO disorder; defective medium-chain FAO
SCAD deficiency	<i>ACADS</i>	SCAD	Deficient short-chain FAO
ACAD9 deficiency	<i>ACAD9</i>	ACAD9	Involved in FAO and amino acid catabolism; mitochondrial dysfunction
LCHAD deficiency	<i>HADHA</i>	LCHAD	Subunit of MTP; impaired long-chain hydroxyacyl-CoA oxidation
MTP deficiency	<i>HADHA, HADHB</i>	MTP	Combined enzyme defect; heterocomplex of HADHA/HADHB subunits
SCHAD deficiency	<i>HADH (HADHSC)</i>	SCHAD	Impaired mitochondrial FAO of hydroxyacyl-CoA
MADD (glutaric aciduria type II)	<i>ETFA, ETFB, ETFDH</i>	ETF, ETFDH	Disrupted electron transfer to respiratory chain in FAO

ACAD9 – Acyl-CoA dehydrogenase 9; ATGL – Adipose triglyceride lipase; CACT – Carnitine-acylcarnitine translocase; CGI-58 – Comparative gene identification-58 (also known as ABHD5); CPT II – Carnitine palmitoyl-transferase II; ETF – Electron transfer flavoprotein; ETFDH – Electron transfer flavoprotein dehydrogenase; FA – Fatty acids; FAO – Fatty acid oxidation; LCAD – Long-chain acyl-CoA dehydrogenase; LCHAD – Long-chain 3-hydroxyacyl-CoA dehydrogenase; MADD – Multiple acyl-CoA dehydrogenase deficiency; MCAD – Medium-chain acyl-CoA dehydrogenase; MTP – Mitochondrial trifunctional protein; NLSD-I – Neutral lipid storage disease type I; NLSD-M – Neutral lipid storage disease type M; OCTN2 – Organic cation/carnitine transporter 2; PCD – Primary carnitine deficiency; SCAD – Short-chain acyl-CoA dehydrogenase; SCHAD – Short-chain L-3-hydroxyacyl-CoA dehydrogenase; VLCAD – Very-long-chain acyl-CoA dehydrogenase.

NLSD-I usually involves only mild myopathy but is primarily characterized by generalized ichthyosis (dry, scaly skin) beginning in early infancy. Other associated features may include global developmental delay, hepatomegaly, sensorineural hearing loss, peripheral neuropathy, cataracts, nystagmus, and retinal abnormalities<sup>2</sup>.

*LPIN1* encodes lipin-1, a phosphatidic acid phosphatase expressed in adipose tissue and skeletal muscle. It plays a key role in triglyceride synthesis and lipid metabolism, as well as in nuclear gene expression regulation<sup>18</sup>. Biallelic mutations in *LPIN1* cause a myopathic disorder typically beginning in early childhood, characterized by acute recurrent episodes of rhabdomyolysis triggered by metabolic stress, with normal function between attacks. Some patients may develop mild proximal muscle weakness over time.

Lastly, biallelic mutations in the *SLC25A20* gene (OMIM #212138) cause carnitine-acylcarnitine translocase (CACT) deficiency<sup>19</sup>. CACT is part of the SLC25 mitochondrial carrier family. It catalyzes the bidirectional transport of carnitine back into the cytoplasm and of acylcarnitine esters (fatty acids bound to carnitine) into the mitochondrial matrix<sup>4</sup>.

With just over 100 individuals reported worldwide<sup>20</sup>, CACT deficiency typically manifests in the neonatal period or early infancy with a severe clinical presentation, including hypotonia, metabolic crisis, cardiomyopathy, life-threatening arrhythmias, and hepatomegaly. Newborn screening programs are available in some countries to detect CACT disorder<sup>21</sup>. Later-onset forms are milder and may present with muscle weakness, fatigue, recurrent episodes of hypoketotic hypoglycemia, and less pronounced or absent cardiac involvement<sup>2</sup>.

### LM Due to Impaired Enzymes/Proteins Acting Inside the Mitochondrion

Another important gene involved in the transport of long-chain fatty acids across the inner mitochondrial membrane is *CPT2*, which encodes carnitine palmitoyltransferase II, with an estimated prevalence of 1-9/100,000 people<sup>22</sup>. Biallelic (homozygous or compound heterozygous) mutations in this gene cause carnitine palmitoyl transferase (CPT) II deficiency<sup>23</sup>. Newborn screening programs have been implemented to detect this disease<sup>24</sup>. There are three main clinical presentations:

- A severe neonatal form, typically fatal due to respiratory distress and metabolic failure;
- An infantile form, characterized by a hepato-cardio-muscular phenotype, which is still associated with high mortality if untreated;
- An adult-onset myopathic form<sup>25</sup>, which usually presents in adolescence with episodes of recurrent exercise-induced (as well as stress, infection, fasting, or cold-exposure related) muscle pain and weakness, culminating sometimes in rhabdomyolysis and myoglobinuria. Usually, no specific signs of myopathy are detectable between attacks. Age at diagnosis can range from 7 to 62 years<sup>26,27</sup>.

The myopathic form of CPT II deficiency is the most common hereditary cause of myoglobinuria, with males more likely affected than females<sup>25</sup>. This gender predominance may be due to hormonal factors<sup>28</sup> or at least partially justified by women's lower susceptibility to myoglobinuria, meaning they may remain undiagnosed. From a genetic point-of-view, the most common variant in the myopathic form of CPT II deficiency is the p.Ser113Leu variation, accounting for 60% of pathogenic alleles<sup>25</sup>; some heterozygous (carriers) individuals have been described<sup>29-32</sup>, exhibiting an intermediate biochemical phenotype (with markedly reduced enzyme activity) though they generally do not display overt symptoms.

Acyl-CoA dehydrogenases (ACADs) are flavoenzymes responsible for the first step of  $\beta$ -oxidation, catalyzing the dehydrogenation of acyl-CoA esters to enoyl-CoA. ACAD-related diseases, which result from the accumulation of specific acyl-CoA intermediates and impaired energy production, can be classified into five groups according to the chain length or structure of the affected acyl-CoA:

- Very long-chain acyl-CoA dehydrogenase (VLCAD)
- Long-chain acyl-CoA dehydrogenase (LCAD)
- Medium-chain acyl-CoA dehydrogenase (MCAD)
- Short-chain acyl-CoA dehydrogenase (SCAD)
- Acyl-CoA dehydrogenase 9 (ACAD9)

Identified also by implemented newborn screening<sup>33</sup>, VLCAD and LCAD deficiencies are caused by biallelic mutations in the *ACADVL* and *ACADL* genes, respectively<sup>34</sup>. While they often present with similar clinical features, LCAD deficiency is extremely rare in humans and is frequently considered a misdiagnosis of VLCAD deficiency, based on multiple reports.

Detected by newborn screening programs<sup>35</sup>, MCAD deficiency, caused by mutations in the *ACADM* gene, is the most common autosomal recessive FAO disorder<sup>36</sup>, with a worldwide birth prevalence of 1 in 15,000<sup>37</sup>.

Mutations in *ACADS* result in SCAD deficiency, which generally presents with a milder phenotype<sup>38</sup>.

As with other disorders in this group, clinical manifestations may include:

- A severe neonatal form with metabolic decompensation (except SCAD, which usually has a more benign prognosis);
- An infantile hepatic form;
- A later-onset, milder myopathic form<sup>39</sup>.

In MCAD deficiency, recurrent episodes of rhabdomyolysis have also been reported<sup>40</sup>, particularly triggered by alcohol consumption.

ACAD9 is involved in the oxidation of long-chain fatty acids (similar to VLCAD) and also plays a key role in the assembly of mitochondrial complex I. Deficiency of this enzyme leads to ACAD9-related disease, characterized by cardiomyopathy, muscle weakness, and exercise intolerance, often accompanied by severe intellectual disability and developmental delay<sup>41</sup>.

The mitochondrial trifunctional protein (MTP) is a multienzyme complex composed of four  $\alpha$  and four  $\beta$  subunits located in the inner mitochondrial membrane, encoded by the nuclear genes *HADHA* and *HADHB*. It catalyzes three sequential reactions in the  $\beta$ -oxidation of long-chain fatty acids:

- Long-chain enoyl-CoA hydratase
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)
- 3-ketoacyl-CoA thiolase

Deficiency in MTP can result from either:

- Isolated LCHAD deficiency due to biallelic mutations in *HADHA*
- Generalized MTP deficiency due to mutations in both *HADHA* and *HADHB*<sup>42</sup>

Generalized MTP deficiency is typically associated with a more severe phenotype, with onset in the first days of life. In contrast, LCHAD deficiency may present hepatic and cardiac manifestations in infancy and may also include specific complications such as progressive retinopathy and peripheral axonal neuropathy. Both forms can also present with later-onset myopathic phenotypes. The combined prevalence of MTP and LCHAD deficiency is estimated to be 1.02 per 100,000 live births worldwide<sup>43</sup>, detectable by newborn screening programs<sup>44</sup>.

Short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency is a recessive disorder caused by mutations in the *HADH* (also referred to as *HADHSC*) gene. This gene encodes the SCHAD enzyme, which catalyzes the third step in  $\beta$ -oxidation, the conversion of short-chain 3-hydroxyacyl-CoA to 3-ketoacyl-CoA for fatty acids with 4-10 carbons<sup>45</sup>.

Unlike other  $\beta$ -oxidation disorders, SCHAD deficiency primarily presents with hyperinsulinism since SCHAD also regulates insulin secretion in pancreatic  $\beta$ -cells, rather than the typical hypoketotic hypoglycemia.

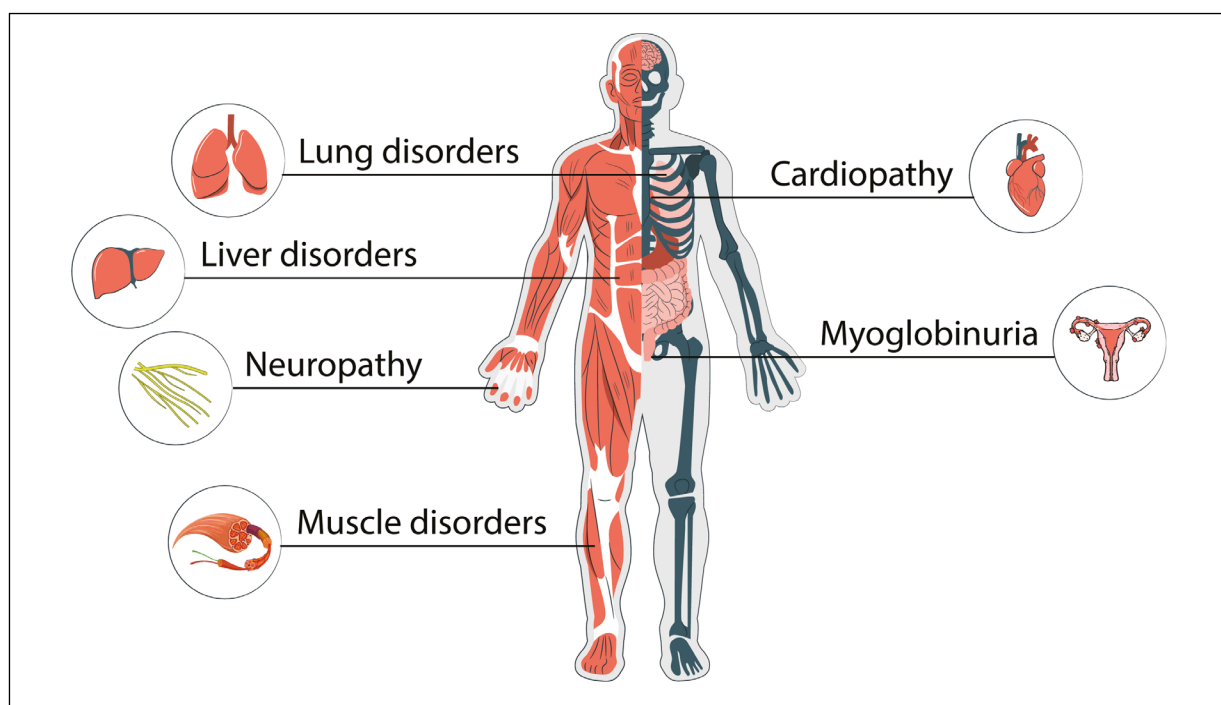
Electron transfer flavoprotein (ETF) is a heterodimer composed of *ETF A* and *ETF B* subunits, which functions together with ETF dehydrogenase (*ETF DH*), also known as ETF-ubiquinone oxidoreductase or ETF-QO. These proteins link substrate oxidation to ATP production by transferring electrons from acyl-CoA dehydrogenases to the mitochondrial respiratory chain.

Mutations in this system lead to multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric aciduria type II (GA-II)<sup>46</sup>. The phenotype is broad due to impaired metabolism of fatty acids, branched-chain amino acids, and other substrates.

- The severe neonatal and milder infantile forms are usually associated with biallelic mutations in *ETF A* and *ETF B*. They often present with characteristic features, such as a “sweaty feet” odor, caused by the accumulation of organic acids and congenital dysmorphisms, in addition to metabolic crises.
- The adult-onset form typically manifests as episodic metabolic crisis (vomiting, nonketotic hypoglycemia, metabolic acidosis, and liver dysfunction) or progressive muscle weakness, exercise intolerance, and myalgia. Weakness typically affects the proximal and neck muscles, leading to bent spine syndrome and dropped-head as possible onset manifestations<sup>47</sup>. Some cases may mimic Guillain-Barré syndrome due to subacute metabolic decompensation and rapidly progressive respiratory failure<sup>48</sup>, while others may also develop a severe sensory neuropathy, causing numbness of the extremities and sensory ataxia, which do not usually respond to supplementary riboflavin treatment<sup>49</sup>. Male patients with adult-onset MADD are more common than female patients, and ethnicity (East Asian)<sup>50</sup> was proven to be a factor influencing the male-to-female ratio in late-onset cases.

In the process of differential diagnosis, some hereditary disorders of riboflavin metabolism presenting with a biochemical profile similar to MADD must be taken into account. These include MADD-like illness due to *FLAD1* gene mutations and Brown-Vialetto-Van Laere syndrome due to *SLC52A2* and *SLC52A3* gene mutations. In both cases, specific clinical features can help to distinguish between these conditions, such as swallowing, speech and respiratory difficulties in the former and cranial nerve involvement (deafness, bulbar palsy) in the latter. Recently, an acquired form of MADD caused by taking sertraline has been reported<sup>51</sup> in some patients. In these cases, discontinuing sertraline and undergoing riboflavin treatment both showed beneficial effects, improving the acylcarnitine profile, alleviating clinical symptoms, normalising creatine kinase (CK) levels, and improving muscle biopsy findings.

Key clinical signs and symptoms that may aid in diagnostic suspicion during adulthood are illustrated in Figure 2.



**Figure 2.** Key clinical signs and symptoms that may aid in diagnostic suspicion during adulthood.

## DIAGNOSTIC APPROACHES

Blood carnitine and acylcarnitine levels, along with urinary organic acid profiles, are common biochemical tests performed in suspected cases of LM; however, only genetic analysis can provide a definitive diagnosis<sup>52</sup>.

Depending on the specific disorder, characteristic biochemical alterations may be observed. For instance, in MADD, total carnitine levels are typically low, while acylcarnitines of all chain lengths (C4–C18) are elevated<sup>6</sup>. Elevated plasma levels of long-chain acylcarnitines (C14–C18) are commonly found in CPT II deficiency, VLCAD, and LCHAD<sup>1,53</sup>. These acylcarnitines can also be measured using tandem mass spectrometry (TMS) on dried blood spots<sup>52</sup>.

Dicarboxylic aciduria, indicating a compensatory activation of omega-oxidation in peroxisomes, is typically present in several of these disorders (e.g., *LPIN1*-related myopathy, MADD).

In MCAD deficiency, increased levels of octanoyl- and decanoylcarnitine can be detected in both blood and urine, while plasma carnitine levels are usually decreased. For SCAD deficiency, elevated concentrations of ethylmalonic and methylsuccinic acids in urine, as well as a high plasma level of C4 acylcarnitine species, are key diagnostic markers<sup>52</sup>.

PCD is typically characterized by a marked reduction in carnitine levels across all tissues (heart, muscle, liver) and plasma, accompanied by increased urinary carnitine excretion due to impaired renal reabsorption. Plasma total and free carnitine levels are often less than 10% of normal values, while levels in muscle tissue may be reduced to below 5%<sup>12</sup>.

During metabolic crises, which are common in many of these myopathies, typical biochemical abnormalities include:

- Elevated creatine kinase (CK),
- Hyperammonemia (resulting from impaired ATP production affecting the urea cycle),
- Lactic acidosis (due to increased reliance on glycolysis in the absence of fatty acid oxidation), and
- Elevated transaminases, reflecting hepatic involvement.

When NLSL is suspected, a simple and cost-effective screening method is light microscopic analysis of a peripheral blood smear, which may reveal intracytoplasmic lipid droplets in leukocytes (especially neutrophils, but also occasionally monocytes or eosinophils), a finding known as “Jordan’s anomaly” (named after Dr. June K. Jordan, who first described it in 1953)<sup>53</sup>. However, this finding lacks absolute specificity, as similar changes may occur secondary to prolonged lipid infusions (e.g., during parenteral nutrition).

Muscle biopsy remains a valuable tool for diagnosing LM, offering direct evidence of histopathological and biochemical changes in skeletal muscle. Common findings include:

- Excessive lipid droplet accumulation in muscle fibers, highlighted by Oil Red O or Sudan Black staining (e.g., in PCD, NLSL, VLCAD, MADD);
- Fiber-type specificity, with lipid deposition predominantly affecting type I (slow-twitch, oxidative) fibers, which depend heavily on fatty acid metabolism;
- Occasional muscle fiber necrosis, regeneration, and inflammatory changes (notably during rhabdomyolysis);
- Mitochondrial abnormalities, such as ragged red fibers or cytochrome-c-oxidase (COX)-negative fibers, are observed in disorders like MADD, VLCAD, LCHAD, or MTP deficiencies<sup>16,52,54,55</sup>.

Muscle MRI is also helpful in the diagnostic process, providing a comprehensive view of muscle involvement and detecting patterns of fat infiltration, edema, and atrophy<sup>1,39</sup>. Typical imaging patterns involve the gluteus minimus, semimembranosus, soleus, and medial gastrocnemius muscles in the lower limbs (with a predominance in the posterior leg and thigh) and the infraspinatus muscle in the upper limbs. A characteristic “patchy” pattern of fatty replacement is often noted<sup>56</sup>. MRI also reveals increased T2-weighted or STIR signal intensity, reflecting acute or subacute muscle damage (as seen during rhabdomyolysis)<sup>57</sup>.

Moreover, MRI serves as a valuable tool for monitoring disease progression, quantifying fat infiltration, evaluating post-crisis recovery (e.g., resolution of edema), and even assessing therapeutic response, such as reduced fat infiltration in riboflavin-responsive MADD.

## TREATMENT AND MANAGEMENT

Treatment strategies for LM are primarily supportive and preventive, as evidence-based therapies remain limited. As summarized in Table 2, most recommendations are applicable across LM subtypes and focus on avoiding precipitating factors, such as prolonged fasting, sustained aerobic exercise (>30 minutes), infections, cold exposure and certain medications (e.g., nonsteroidal anti-inflammatory drugs). In cases of rhabdomyolysis, emergency management involves aggressive intravenous hydration with isotonic saline and glucose-containing solutions, along with close monitoring of renal function, electrolyte balance, and cardiac status. Long-term care may include dietary modifications, pharmacologic supplementation, and, in selected cases, targeted therapies tailored to the specific metabolic defect<sup>1</sup>.

In PCD, oral L-carnitine supplementation is an effective treatment. When initiated early, before irreversible damage occurs, it leads to significant improvement in both skeletal myopathy and cardiomyopathy. Management also involves avoiding drugs that promote carnitine loss in urine, such as pivampicillin<sup>58</sup>.

In CPT II deficiency, as in other disorders involving secondary carnitine deficiency and metabolic crises, recommendations include carnitine supplementation to enhance fatty acid transport, high-carbohydrate intake before and during prolonged exercise, and frequent meals to avoid fasting-induced stress<sup>59</sup>.

Management of CACT deficiency may also include supplementation with medium-chain triglycerides (MCTs) and essential polyunsaturated fatty acids<sup>4</sup>.

Currently, no curative treatment exists for NLSL. The therapeutic approach is limited to a low-fat diet, MCT supplementation, and carnitine administration<sup>1</sup>.

In MADD, riboflavin supplementation has shown clinical benefit, especially when combined with a low-fat diet, carnitine, and coenzyme Q10 (CoQ10)<sup>10</sup>. Riboflavin has also demonstrated some benefit in ACAD9 deficiency.

Patients with MTP deficiency or isolated LCHAD deficiency may benefit from docosahexaenoic acid (DHA) supplementation, triheptanoin, and peroxisome proliferator-activated receptor (PPAR) agonists. Treatment strategies are often personalized based on the presence and severity of systemic manifestations, such as peripheral neuropathy or retinopathy<sup>1</sup>.

**Table 2.** Treatment and preventive strategies in primary lipid myopathies.

Disorder	Treatment Strategies	Preventive Measures
<b>I. Disorders causing primary carnitine deficiency</b>		
PCD	Oral L-carnitine supplementation (100-200 mg/kg/day divided 3x/day) for skeletal myopathy and cardiomyopathy	Avoid drugs that promote carnitine loss (e.g., pivampicillin), prevent fasting, manage infections
<b>II. Disorders involving cytoplasmic enzymes or transporters</b>		
NLSD-M, NLSD-I	Low-fat diet, medium-chain triglyceride supplementation, carnitine administration	Avoid triggers of metabolic stress, prevent excessive fat intake
CACT deficiency	Medium-chain triglycerides and essential poly-unsaturated fatty acid supplementation	Avoid fasting, manage infections and stress
<b>III. Disorders involving mitochondrial FAO</b>		
CPT II deficiency	Carnitine supplementation, high-carbohydrate (70%) and low-fat (<20%) intake before exercise, frequent meals	Avoid fasting, intense exercise, infections, and cold exposure
MADD	Riboflavin supplementation (100-300 mg daily), low-fat diet, carnitine supplementation (50-100 mg/kg daily divided into three doses) in those with carnitine deficiency, and coenzyme Q10 supplements (60-240 mg daily into two divided doses)	Prevent metabolic stress, maintain hydration during rhabdomyolysis
VLCAD deficiency	High-carbohydrate diet, frequent meals, avoid fasting	Prevent metabolic stress, infections, and cold exposure
LCHAD Deficiency	Docosahexaenoic acid supplementation, triheptanoin, PPAR agonists	Avoid fasting, infections, and metabolic stress
MTP deficiency	Docosahexaenoic acid supplementation, triheptanoin, PPAR agonists	Avoid fasting, infections, and cold exposure
SCHAD deficiency	Manage hyperinsulinism, dietary modifications	Avoid fasting and metabolic triggers

CACT – Carnitine-acylcarnitine translocase; CPT II – Carnitine palmitoyltransferase II; LCHAD – Long-chain 3-hydroxyacyl-CoA dehydrogenase; MADD – Multiple acyl-CoA dehydrogenase deficiency; MTP – Mitochondrial trifunctional protein; NLSD-I – Neutral lipid storage disease type I; NLSD-M – Neutral lipid storage disease type M; PCD – Primary carnitine deficiency; SCHAD – Short-chain L-3-hydroxyacyl-CoA dehydrogenase; VLCAD – Very-long-chain acyl-CoA dehydrogenase.

Emerging therapeutic approaches include molecular strategies aimed at enzyme correction, such as gene therapy and enzyme replacement therapy. For instance, in a murine model<sup>60</sup> of VLCAD deficiency, the use of adeno-associated virus serotype 9 (AAV9) to deliver a functional copy of the gene resulted in long-term correction of the metabolic defect, improved cardiac function and increased survival.

## EXPERT OPINION

Given the clinical heterogeneity and the absence of specific features (with some phenotypes shared by multiple genetic causes), diagnostic delay remains a significant challenge in lipid myopathies, one that is only partially addressed by newborn screening. Late diagnosis, often triggered by the onset of an acute metabolic crisis, can result in irreversible deficits and, in rare cases, reduced survival. Future perspectives will focus on advanced models to investigate the mechanisms of tissue-specific damage, along with the discovery of biomarkers and the development of imaging techniques to improve early detection and monitoring. In the era of gene therapy, preclinical studies have laid the groundwork for gene delivery in lipid myopathies.

## CONCLUSIONS

Primary lipid myopathies are rare, genetically heterogeneous disorders of fatty acid metabolism that often present with nonspecific symptoms such as muscle weakness, exercise intolerance, or metabolic crises. Due to their clinical variability, diagnosis is frequently delayed. Early recognition is critical, as timely interventions, such as dietary modifications, cofactor supplementation, and avoidance of metabolic stress, can significantly improve outcomes.

Although current treatments are largely supportive, advances in molecular diagnostics and emerging therapies, including gene-based approaches, offer promising avenues for personalized care. Increased clinical awareness and multidisciplinary collaboration are essential to improve diagnosis, management, and long-term prognosis in affected individuals.

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