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Dihydrolipoamide Dehydrogenase Deficiency

Synonyms: DLD Deficiency, E3 Deficiency

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Summary

Clinical characteristics

The phenotypes of dihydrolipoamide dehydrogenase (DLD) deficiency are an overlapping continuum that ranges from early-onset neurologic manifestations to adult-onset liver involvement and, rarely, a myopathic presentation. Early-onset DLD deficiency typically manifests in infancy as hypotonia with lactic acidosis. Affected infants frequently do not survive their initial metabolic decompensation, or die within the first few years of life during a recurrent metabolic decompensation. Children who live beyond the first two to three years frequently exhibit growth deficiencies and residual neurologic deficits (intellectual disability, spasticity, ataxia, and seizures). In contrast, isolated liver involvement can present as early as the neonatal period and as late as the third decade. Evidence of liver injury/failure is preceded by nausea and emesis and frequently associated with encephalopathy and/or coagulopathy. Acute metabolic episodes are frequently associated with lactate elevations, hyperammonemia, and hepatomegaly. With resolution of the acute episodes affected individuals frequently return to baseline with no residual neurologic deficit or intellectual disability. Liver failure can result in death, even in those with late-onset disease. Individuals with the myopathic presentation may experience muscle cramps, weakness, and an elevated creatine kinase.

Diagnosis/testing

The diagnosis of dihydrolipoamide dehydrogenase deficiency (DLD) is established in a proband with suggestive clinical and supportive laboratory findings and/or by identification of biallelic pathogenic variants in *DLD*.

Management

Treatment of manifestations:

- Routine daily treatment for those with the early-onset neurologic presentation: protein intake at approximately recommended dietary allowance (RDA); if there is evidence of significant hyperleucinosis, protein intake should consist of branched-chain amino acid (BCAA)-free powder formula with 2-3

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g/kg/day natural protein; ketogenic/high-fat diet; dichloroacetate (DCA) supplementation (50-75 mg/kg/day); feeding therapy and consideration of gastrostomy tube for persistent feeding issues; standard treatment for developmental delay / intellectual disability, cardiac dysfunction, and vision impairment / optic atrophy.

- Acute inpatient treatment for those with early-onset neurologic presentation: address any precipitating factors (infection, fasting, medications); D_{10} (half or full-normal saline) with age-appropriate electrolytes; consideration of bicarbonate therapy for those with severe metabolic acidosis; withholding of protein for a maximum of 24 hours; consideration of renal replacement therapies; total protein intake at RDA; if there is evidence of significant hyperleucinosis, protein intake should be adjusted to provide 2-3.5 g/kg/day as BCAA-free amino acids; isoleucine and valine supplements; maintain serum osmolality within the normal reference range; levocarnitine (IV or PO) 50-100 mg/kg/day divided three times per day; continuation of DCA; standard therapy for seizures.
- For hepatic presentation: removal or treatment of precipitating factors; dextrose-containing IV fluids (6-8 mg/kg/min) with age-appropriate electrolytes and/or frequent feedings; consider correction of metabolic acidosis using sodium bicarbonate; consideration of DCA and/or dialysis; consideration of fresh frozen plasma for coagulopathy.
- For the myopathic presentation: At least one affected individual with severe exercise intolerance responded well to riboflavin supplementation (220 mg/day).

Prevention of primary manifestations: No compelling evidence exists for the prevention of acute episodes, despite multiple attempted dietary strategies and medications. Provide protein intake at or around recommended dietary allowance and titrate based on growth and plasma amino acid values; supplementation with levocarnitine, if deficient.

Prevention of secondary complications: DCA has been associated with the development of peripheral neuropathy; thus, individuals receiving this medication require close monitoring.

Surveillance: Measurement of growth parameters and evaluation of nutritional status and safety of oral intake at each visit; full amino acid profile (from plasma or filter paper) weekly or twice weekly in rapidly growing infants and routinely in older individuals; at least monthly visit with a metabolic specialist in infancy; assessment of developmental milestones at each visit or as needed; physical examination and/or ultrasound to assess liver size, measurement of liver transaminases and liver synthetic function, and assessment for peripheral neuropathy at each visit; echocardiogram at least annually or based on clinical status; ophthalmologic evaluation as clinically indicated.

Agents/circumstances to avoid: Fasting, catabolic stressors, and extremes of dietary intake until dietary tolerance/stressors are identified; liver-toxic medications.

Evaluation of relatives at risk: Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of DLD deficiency and to avoid risk factors that may precipitate an acute event. For at-risk newborn sibs when molecular genetic prenatal testing was not performed: in parallel with NBS either test for the familial *DLD* pathogenic variants or measure plasma lactate, plasma amino acids, and urine organic acids.

Genetic counseling

DLD deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *DLD* pathogenic variants in the family are known.

Diagnosis

Dihydrolipoamide dehydrogenase (DLD) functions as the E3 subunit of three mitochondrial enzyme complexes: branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, α-ketoglutarate dehydrogenase (αKGDH) complex, and pyruvate dehydrogenase (PDH) complex [Chuang et al 2013]. The E3 subunit is responsible for the reoxidation of the reduced lipoyl moiety of the E2 subunit. Although DLD also functions as the L protein of the glycine cleavage system, pathogenic variants in *DLD* do not appear to impair the function of this system in vivo.

The phenotypic spectrum of DLD deficiency includes an early-onset neurologic presentation, a primarily hepatic presentation, and a primarily myopathic presentation.

No formal clinical diagnostic criteria have been established for dihydrolipoamide dehydrogenase (DLD) deficiency.

Suggestive Findings

The diagnosis of dihydrolipoamide dehydrogenase (DLD) deficiency **should be suspected** in individuals with the following clinical and supportive laboratory findings.

Clinical findings

- **Neurologic.** Early-onset hypotonia, lethargy, and emesis
  - In untreated infants, manifestations progress to deepening encephalopathy (lethargy, tone abnormalities, feeding difficulties, decreased level of alertness, and occasionally seizures) and eventual death.
  - Neurologic impairment presents in those who survive the first year of life.
- **Hepatic.** Recurrent liver injury/failure frequently preceded by nausea and emesis
  - Age of onset ranges from the neonatal period to the third decade.
  - Individuals with the hepatic form typically have normal intellect with no residual neurologic deficit between acute metabolic episodes unless neurologic damage has occurred.
- **Myopathic.** Muscle cramps, weakness, and an elevated creatine kinase

  While muscle involvement is the main feature in previously reported individuals, additional findings include intermittent acidosis and hepatic involvement [Quintana et al 2010, Carrozzo et al 2014].

Supportive laboratory findings

- **Newborn screening (NBS).** Citrulline is elevated on NBS dried blood spot [Haviv et al 2014, Quinonez et al 2014].

  Note: (1) Newborn screening has failed to identify asymptomatic individuals with DLD deficiency when either dried blood spot citrulline or leucine is used as a primary screening analyte; (2) Individuals with an early-onset or hepatic presentation only occasionally have biochemical evidence of dysfunctional branched chain amino acid (BCAA) metabolism (i.e., elevations of allo-isoleucine and branched chain ketoacids; see Table 1), making leucine an unreliable marker for screening; (3) DLD deficiency is not listed as a condition on the differential diagnosis for an increased citrulline on the ACMG ACT Sheet and is not currently reported on most NBS panels.
- Abnormal laboratory findings typically associated with the **neurologic presentation**:
  - Metabolic acidosis. Arterial pH <7.35 or venous pH <7.32 and serum bicarbonate <22 mmol/L in children and adults or <17 mmol/L in neonates

- Hypoglycemia. <40 mg/dL (<2.2 mmol/L)
- Other metabolic abnormalities listed in Table 1

- Laboratory findings typically associated with the **hepatic presentation**:
  - Elevated lactate level (>2.2 µmol/L)
  - Isolated elevated transaminases to fulminant hepatic failure
  - Absence of other metabolic abnormalities (See Table 1.)
- Laboratory findings typically associated with the **myopathic presentation**:
  - Normal-to-elevated serum creatinine kinase (CK) level, up to 20 times the normal range during acute episodes (<192 U/L) [Carrozzo et al 2014]
  - Occasionally elevated transaminases, lactate, and other metabolic abnormalities (See Table 1.)

Table 1. Metabolic Abnormalities in DLD Deficiency by Presentation

Metabolite	Presentation			Normal
	Neurologic	Hepatic	Myopathic	
Plasma lactate	↑	↑	Normal to ↑	<2.2 µmol/L
Urine α-ketoglutarate	Normal to ↑	Typically normal	Normal to ↑	• Neonates: 4-524 mmol/mol creatinine • Children: 36-117 mmol/mol creatinine • Adults: 4-74 mmol/mol creatinine
Urine branched-chain ketoacids	Absent to ↑	Typically absent	Absent to ↑	• Neonates: <7 mmol/mol creatinine • All other ages: not detectable
Plasma leucine	Normal to ↑	Typically normal	Normal to ↑	• Infants: 46-147 µmol/L • Children: 30-246 µmol/L • Adolescents-adults: 86-206 µmol/L
Plasma isoleucine	Normal to ↑	Typically normal	Normal to ↑	• Infants: 12-77 µmol/L • Children: 6-122 µmol/L • Adolescents-adults: 34-106 µmol/L
Plasma valine	Normal to ↑	Typically normal	Normal to ↑	• Infants: 79-217 µmol/L • Children: 132-480 µmol/L • Adolescents-adults: 155-343 µmol/L
Plasma allo-isoleucine	Normal to ↑	Typically normal	Normal to ↑	<5 µmol/L

Establishing the Diagnosis

The diagnosis of dihydrolipoamide dehydrogenase deficiency (DLD) **is established in a proband** with suggestive clinical and supportive laboratory findings (see Table 1) AND/OR by identification of biallelic pathogenic variants in *DLD* (see Table 2).

Note: The presence of decreased DLD enzymatic activity in fibroblasts, lymphocytes, or liver tissue can also be used to establish the diagnosis but is not recommended as a first-line test, given the general availability of molecular genetic testing.

When laboratory findings suggest the diagnosis of DLD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing. Sequence analysis of *DLD* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants.

- Targeted analysis for the c.685G>T (p.Gly229Cys) pathogenic variant may be considered first in individuals of Ashkenazi Jewish ancestry.

- Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.
- If only one or no variant is detected by the sequencing method used, the gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications may be considered.

A multigene panel that includes *DLD* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 2. Molecular Genetic Testing Used in Dihydrolipoamide Dehydrogenase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DLD	Sequence analysis [3]	42/43 (98%) [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
	Targeted analysis for pathogenic variants [7]	See footnote 8.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Quintana et al [2010], Brassier et al [2013], Quinonez et al [2013], Carrozzo et al [2014], Haviv et al [2014], Bravo-Alonso et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No deletions or duplications involving *DLD* have been reported to cause dihydrolipoamide dehydrogenase deficiency.
7. Variant panels may differ by laboratory.
8. The c.685G>T (p.Gly229Cys) pathogenic variant is common in Ashkenazi Jews (see Prevalence).

Clinical Characteristics

Clinical Description

Persons with dihydrolipoamide dehydrogenase (DLD) deficiency exhibit variable phenotypic and biochemical consequences based on the three affected enzyme complexes. While the spectrum of disease ranges from early-onset neurologic manifestations to isolated adult-onset liver involvement, it represents a continuum and differentiation between discretely defined presentations can occasionally be difficult.

Early-Onset Neurologic Presentation

The most frequent clinical finding in early-onset DLD deficiency is that of a hypotonic infant with lactic acidosis (Table 3). Affected infants frequently do not survive their initial metabolic decompensation or die within the first one to two years of life during a recurrent metabolic decompensation.

Children who live beyond the first two to three years frequently exhibit growth deficiencies and residual neurologic deficits including intellectual disability, spasticity (hypertonia and/or hyperreflexia), ataxia, and seizures. Typically, seizures are generalized tonic-clonic and occur during episodes of metabolic decompensation and not during periods when affected individuals are metabolically stable [Quinonez et al 2013]. Medication-refractory epilepsy has been seen in one affected individual with neurologic impairment secondary to metabolic decompensation [Author, personal observation]. Of note, normal intellectual functioning has been reported in individuals with certain genotypes (see Genotype-Phenotype Correlations).

Table 3. Features of the Early-Onset Neurologic Phenotype

Disease Features		Frequency [1]	%
Clinical presentation [2]	Hypotonia	16/25	64
	Developmental delay	12/25	48
	Emesis	12/25	48
	Hepatomegaly	10/25	40
	Lethargy	8/25	32
	Seizures	7/25	28
	Spasticity (hypertonia &/or hyperreflexia)	7/25	28
	Leigh syndrome phenotype	6/25	24
	Failure to thrive	6/25	24
	Microcephaly	5/25	20
	Vision impairment	4/25	16
	Ataxia	3/25	12
	Cardiac involvement	3/25	12
Laboratory abnormalities	Metabolic acidosis [3]	22/25	88
	↑ plasma lactate [4]	18/25	72
	↑ urine α-ketoglutarate [4]	13/25	52
	Hypoglycemia [5]	12/25	48
	↑ plasma BCAA [4]	10/25	40
	↑ transaminases	11/25	44
	↑ urine branched-chain ketoacids [4]	7/25	28
	Hepatic failure	5/25	20
	↑ plasma allo-isoleucine [4]	4/25	16
	Low free plasma carnitine [6]	3/25	12
	Hyperammonemia [7]	4/25	16

Includes only individuals biochemically confirmed to have DLD deficiency
BCAA = branched-chain amino acids
1. Quinonez et al [2013], Bravo-Alonso et al [2019]
2. Later physical examination and neurologic findings are likely underrepresented, as children with an early-onset presentation frequently die in the first year(s) of life.
3. Arterial pH <7.35 or venous pH <7.32; serum bicarbonate <22 mmol/L in infants, children, and adults; or <17 mmol/L in neonates
4. See Table 1.
5. Glucose <40 mg/dL
6. Carnitine (free) <38±22
7. Ammonia >100 µmol/L in neonates or >60 µmol/L in infants, children, and adults

Metabolic phenotype. DLD deficiency is associated with recurrent episodes of metabolic decompensation typically triggered by illness/fever, surgery, fasting, or diet (high in fats and/or protein).

- Some affected individuals have experienced worsening of clinical status with high-fat diets [Brassier et al 2013], while others have achieved metabolic control with ketogenic diets (see Management).
- Some individuals with DLD deficiency have features of Leigh syndrome [Quinonez et al 2013]. Leigh syndrome consists of characteristic clinical findings and brain pathology.

  The diagnostic criteria for Leigh syndrome include: (1) progressive neurologic disease with motor and intellectual developmental delay; (2) signs and features of brain stem or basal ganglia disease; (3) elevated lactate levels in the blood or cerebrospinal fluid; and (4) one or more of three features:
  - Characteristic features of Leigh syndrome on neuroradioimaging (symmetric hypodensities in the basal ganglia on computed tomography, or hyperintense lesions on T_2-weighted MRI)
  - Typical neuropathologic changes at postmortem examination
  - Typical neuropathology in a similarly affected sib

Liver abnormalities. Hepatomegaly and liver dysfunction/failure (elevated transaminases, synthetic failure) can occur during acute episodes and occasionally are the cause of death.

- Between acute episodes both liver size and transaminase levels can return to normal.
- Liver biopsies have shown increased glycogen content and mild fibrosis or fatty, acute necrosis with a Reye syndrome-like appearance.

Cardiac dysfunction. Hypertrophic cardiomyopathy was reported in two affected individuals and "myocardial dysfunction" in one.

Hyperammonemia (≤250 µmol/L) is sometimes observed at the time of initial presentation, although this is typically associated with various degrees of hepatic injury/failure [Quinonez et al 2013, Bravo-Alonso et al 2019].

Vision impairment/optic atrophy can occur, with progression to full blindness reported.

Hepatic Presentation

Affected individuals with a primarily hepatic presentation can develop signs and symptoms as early as the neonatal period and as late as the third decade of life [Brassier et al 2013]. Evidence of liver injury/failure (Table 4) is preceded by nausea and emesis and frequently associated with encephalopathy and/or coagulopathy. Liver failure as a cause of death has been reported in multiple affected individuals, including those who presented later in life. The hepatic manifestations of these individuals are typically only present during acute episodes, while other findings (muscle cramps, behavioral disturbances, and vision loss) have been reported when affected individuals are clinically well.

Table 4. Features of the Hepatic Phenotype

Disease Features		Frequency [1]	%
Clinical presentation	Nausea/emesis	13/13	100
	Hepatomegaly	9/13	69
	Hepatic encephalopathy	7/13	54
	Muscle cramps	3/13	23
	Behavioral disturbances	1/13	8
	Optic atrophy	1/13	8

Table 4. continued from previous page.

Disease Features		Frequency [1]	%
Laboratory abnormalities	↑ transaminases	13/13	100
	Coagulopathy	11/13	85
	↑ lactate [2]	10/13	77
	Hyperammonemia [3]	8/13	62
	Hypoglycemia [4]	5/13	38
	↑ urine α-ketoglutarate [2]	2/13	15
	Low carnitine [5]	1/13	8
	↑ plasma BCAA [2]	1/13	8

Includes only individuals biochemically confirmed to have DLD deficiency
BCAA = branched-chain amino acids
1. Brassier et al [2013]
2. See Table 1.
3. Ammonia >100 µmol/L in neonates or >60 µmol/L in infants, children, and adults
4. Glucose <40 mg/dL
5. Carnitine (free) <38±22

Acute metabolic episodes are frequently associated with lactate elevations, hyperammonemia, and hepatomegaly. With resolution of the acute episodes (see Management) affected individuals may return to baseline with normal transaminases, coagulation parameters, mental status, and no residual neurologic deficit or intellectual disability.

Affected individuals frequently experience lifelong recurrent attacks of hepatopathy that decrease with age. Attacks are often precipitated by catabolism, intercurrent illness/fever, and dietary extremes. These individuals additionally are more susceptible to hepatotropic viruses (e.g., Epstein-Barr virus) and medications (e.g., acetaminophen) [Brassier et al 2013, Quinonez et al 2013].

Liver biopsy electron microscopy has shown the presence of lipid droplets [Brassier et al 2013].

Table 3 and Table 4 reveal features common to both the early-onset neurologic presentation and the hepatic presentation (i.e., elevated transaminases, hepatomegaly, and lactate elevations), and differentiation of the two types can be difficult, especially in neonates. To date, the only affected individual with a hepatic phenotype who displayed hypotonia or residual neurologic deficiencies had experienced a severe episode associated with deep coma and residual vision loss and behavioral disturbances. Therefore, the absence of hypotonia and neurologic deficit and the presence of hepatic signs are useful discriminating features.

Myopathic Presentation

Two individuals have been described with a phenotype consisting of primarily myopathic symptoms [Quintana et al 2010, Carrozzo et al 2014]. One of these people additionally exhibited ptosis, weakness, and elevated creatine kinase and lactate [Quintana et al 2010]. The other also experienced early episodes of hypotonia, lethargy, acidosis, and lactic acid elevations without CK elevations. In adolescence this individual developed myalgias, weakness, fatigue, significant hyperCKemia and transaminitis with significant improvement of all signs and symptoms with riboflavin supplementation [Carrozzo et al 2014].

Genotype-Phenotype Correlations

Phenotypic severity is difficult to predict based on genotype and residual enzyme function [Quinonez et al 2013]. However, some correlations have been reported for individuals who have at least one c.685G>T (p.Gly229Cys) pathogenic variant:

- Normal intellectual functioning has been reported in individuals with early-onset disease with compound heterozygosity for the c.685G>T (p.Gly229Cys) pathogenic variant and an additional pathogenic allele.
- All individuals with an exclusively hepatic presentation have been homozygous for the c.685G>T (p.Gly229Cys) pathogenic variant [Brassier et al 2013].

  Note: Individuals homozygous for the c.685G>T (p.Gly229Cys) pathogenic variant were initially thought to have a primarily hepatic presentation. Subsequently, individuals homozygous for c.685G>T (p.Gly229Cys) were found to have the early-onset neonatal neurologic presentation as well.

Nomenclature

DLD deficiency is occasionally referred to as maple syrup urine disease (MSUD) type 3 as it functions as the E3 subunit of BCKDH. Note that MSUD type 1 is caused by biallelic pathogenic variants in *BCKDHA* (E1α) or *BCKDHB* (E1β) and MSUD type 2 is caused by biallelic pathogenic variants in *DBT* (E2). See Maple Syrup Urine Disease.

DLD deficiency may also be referred to as lipoamide dehydrogenase deficiency.

Prevalence

In the Ashkenazi Jewish population, the carrier frequency of the c.685G>T (p.Gly229Cys) pathogenic variant is estimated to be between 1:94 and 1:110 with an estimated disease frequency of 1:35,000 to 1:48,000 [Scott et al 2010]. This is likely an underestimate of disease, as additional pathogenic variants account for DLD deficiency in this population as well [Shaag et al 1999].

The incidence and carrier frequency in other populations are unknown; DLD deficiency is likely very rare.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *DLD*.

Differential Diagnosis

Early-onset neurologic presentation

Table 5. Genes of Interest in the Differential Diagnosis of Dihydrolipoamide Dehydrogenase Deficiency

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder	Distinguishing Features
BCKDHA *BCKDHB* *DBT*	Maple syrup urine disease (MSUD) types 1 & 2	AR	**Age 12-24 hrs.** Maple syrup odor in cerumen, ↑ plasma concentrations of BCAAs [2] & allo-isoleucine, & generalized disturbance of plasma amino acid concentration ratios **Age 2-3 days.** Ketonuria, irritability, & poor feeding **Age 4-5 days.** Deepening encephalopathy manifesting as lethargy, intermittent apnea, opisthotonus, & stereotyped movements (e.g., "fencing" & "bicycling") **Age 7-10 days.** Possible coma & central respiratory failure	• DLD deficiency causes MSUD type 3 & can typically be differentiated from MSUD types 1 & 2 by the presence of severe lactic acidosis, α-ketoglutarate excretion in urine, & liver involvement in DLD deficiency • The maple syrup odor frequently assoc w/MSUD types 1 & 2 is not typically assoc w/DLD deficiency.
BOLA3 *IBA57* *LIAS* *LIPT1* *NFU1*	Defects in lipoic acid metabolism (OMIM 605711, 614299, 614462, 615330, 616299)	AR	Neonatal lactic acidosis & a biochemical phenotype similar to DLD deficiency [3]	Unlike DLD deficiency, children w/defects in lipoic acid metabolism (except LIPT1 deficiency) have ↑ glycine in body fluids.
DLAT *DLD* *PDHA1* *PDHB* *PDHX* *PDK3* *PDP1*	Primary pyruvate dehydrogenase complex deficiency	AR XL [4]	Most commonly presents w/ neurologic impairment, hypotonia, structural brain abnormalities, & lactic acidosis w/a normal lactate:pyruvate ratio [1]	While clinical findings & preliminary lab values are similar, DLD deficiency is often also assoc w/: (a) defective αKGDH w/↑ urine α-ketoglutarate & (b) BCKDH complex dysfunction w/↑ plasma BCAAs & urine branched-chain ketoacids.

αKGDH = α-ketoglutarate dehydrogenase; AR = autosomal recessive; BCAA = branched-chain amino acid; BCKDH = branched-chain α-ketoacid dehydrogenase; DD = developmental delay; DiffDx = differential diagnosis; DLD = dihydrolipoamide dehydrogenase; MOI = mode of inheritance; PDH = pyruvate dehydrogenase; XL = X-linked

1. Patel et al [2012]

2. Leucine, isoleucine, and valine

3. Lipoic acid is the essential cofactor attached to the E2 subunits of BCKDH, αKGDH, and PDH as well as to the H protein of the glycine cleavage system (see Glycine Encephalopathy) [Cameron et al 2011, Mayr et al 2011, Navarro-Sastre et al 2011, Ajit Bolar et al 2013, Haack et al 2013, Soreze et al 2013, Tort et al 2014].

4. PDHA1- and *PDK3*-related primary pyruvate dehydrogenase complex deficiency (PDCD) are inherited in an X-linked manner. Primary PDCD caused by pathogenic variants in *DLAT*, *DLD*, *PDHB*, *PDHX*, or *PDP1* is inherited in an autosomal recessive manner.

Isolated α-ketoglutarate dehydrogenase deficiency (OMIM 203740) has been reported in two sets of consanguineous sibs with choreoathetoid movements, hypotonia, developmental delay, and lactic acidosis. All affected individuals exhibited isolated elevations of α-ketoglutarate in the urine.

Elevated citrulline on newborn screening dried blood spot has been identified in three symptomatic individuals with DLD deficiency [Haviv et al 2014, Quinonez et al 2014]. As recommended by the American College of Medical Genetics (see ACMG ACT Sheet / ACMG Algorithm), other causes of an elevated citrulline on dried blood spot including citrullinemia type I, argininosuccinate lyase deficiency, citrullinemia type II (citrin deficiency), and pyruvate carboxylase deficiency should be investigated.

Isolated liver involvement has a broad differential and an underlying cause is not identified in up to 50% of cases. NBAS deficiency (OMIM 616483) and other inborn errors of metabolism, including fatty acid oxidation disorders (e.g., very long chain acyl-CoA dehydrogenase deficiency, medium-chain acyl-CoA dehydrogenase deficiency, and short-chain acyl-CoA dehydrogenase deficiency), mitochondrial disorders, and disorders of the

carnitine cycle (e.g., systemic primary carnitine deficiency and carnitine palmitoyltransferase II deficiency) should be considered [Haack et al 2015]. A comprehensive biochemical workup followed by genetic testing if indicated will appropriately evaluate for the various genetic conditions in the differential diagnosis.

Management

Consensus recommendations for the management of DLD deficiency do not currently exist. Theoretic difficulties exist for the management of affected individuals based on the various metabolic pathways affected by the three involved enzyme complexes. In practice, these difficulties have been experienced and make empiric treatment recommendations challenging.

When dihydrolipoamide dehydrogenase (DLD) deficiency is suspected during the diagnostic evaluation, treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with dihydrolipoamide dehydrogenase (DLD) deficiency, the evaluations summarized in the following tables (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis of Dihydrolipoamide Dehydrogenase Deficiency in an Ill Neonate

System/Concern	Evaluation	Comment
Metabolic decompensation	Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	Transfer to a specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended)
	STAT blood gas (arterial or venous), ammonia, lactic acid, CK, & glucose	Urgent labs to be obtained if an acute metabolic crisis is suspected
	Plasma free & total carnitine, plasma amino acids, & urine organic acids	To be obtained during a period of acute metabolic decompensation, if possible
Hepatic	Measure liver transaminases (AST, ALT) & assess liver synthetic function.	
	Assessment of liver size	Via physical exam &/or ultrasonography
Neurologic	Evaluate for seizures	Consider EEG if concerned.
Cardiac	Echocardiogram	To assess for cardiac dysfunction & hypertrophy

Table 7. Recommended Evaluations Following Initial Diagnosis of Dihydrolipoamide Dehydrogenase Deficiency in a Stabilized Neonate/Infant

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth parameters	
Neurologic	Neurologic eval	Consider: • Head MRI to assess for brain damage; • EEG if seizures a concern; • Regular developmental assessments to identify impairments resulting from metabolic decompensations.

Table 7. continued from previous page.

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic eval	If concerns for vision loss
Miscellaneous/ Other	Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assessment of parental coping skills & resources

Table 8. Recommended Evaluations Following Initial Diagnosis of Dihydrolipoamide Dehydrogenase Deficiency in an Older Child or Adult

System/Concern	Evaluation	Comment
Hepatic	Measurement of liver transaminases (AST, ALT) & assessment of liver synthetic function	
Eyes	Ophthalmologic eval	If concerns for vision loss or ptosis
Metabolic	• Blood gas (arterial or venous), ammonia, lactic acid, CK, & glucose • Plasma free & total carnitine, plasma amino acids, & urine organic acids	Laboratory studies should be obtained urgently if an acute metabolic crisis is suspected or routinely as part of baseline testing for those w/hepatic or myopathic forms.
Neurologic	Assessment for muscular weakness	If myopathic form is suspected
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

Treatment of Manifestations

Early-Onset Neurologic Presentation

The multiple strategies that have been attempted in children with an early-onset neurologic presentation do not appear to significantly alter the natural history of disease. Even with treatment, children often die in the neonatal/infantile period or, if they survive the initial episode, experience various degrees of chronic neurologic impairment.

Table 9. Routine Daily Treatment in Individuals with Early-Onset Neonatal Dihydrolipoamide Dehydrogenase Deficiency

Principle/Manifestation	Treatment	Consideration/Other
Protein/BCAA restriction [1, 2, 3]	Protein intake at RDA if no hyperleucinosis is present	
	If significant hyperleucinosis is present, consider providing protein that consists of 2-3 g/kg/day from BCAA-free amino acids.	• Leucine tolerance for neonates: 65-85 mg/kg/day • Breast milk or regular infant formula can be used as a natural protein source. • Dried blood spots by overnight mail for monitoring of amino acid concentrations if available (See Surveillance.) [4] • Leucine restriction should be maintained until hyperleucinosis resolves.
Defective carbohydrate oxidation	Ketogenic/high-fat diet [5]	Of 7 persons treated: • 5 had no clinical benefit, & 2 of the 5 experienced ↑ in acidosis & hypoglycemia; [5] • 2 improved clinically. [6]

Table 9. continued from previous page.

Principle/Manifestation	Treatment	Consideration/Other
Inhibition of PDH kinase activity	DCA supplementation (50-75 mg/kg/day)	• 4 of 5 persons treated w/DCA in the literature experienced at least transient ↓s in lactic acid elevations. • Chronic use of DCA can result in polyneuropathy.
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Developmental delay / Intellectual disability	Standard treatment per developmental pediatrician / neurodevelopmental team	Incl PT, OT, & speech therapy as indicated
Cardiac dysfunction	Standard treatment per cardiologist	
Vision impairment / Optic atrophy	Standard treatment per ophthalmologist	

BCAA = branched-chain amino acids; DCA = dichloroacetate; OT = occupational therapy; PDH = pyruvate dehydrogenase; PT = physical therapy; RDA = recommended dietary allowance

1. Recommendations are based on decreased branched-chain α-ketoacid dehydrogenase (BCKDH) complex activity.

2. Restriction of protein to recommended dietary allowances has been attempted with questionable results.

3. Three of the six reported individuals experienced laboratory and/or clinical improvement with the use of protein restriction alone or in combination with medication therapy.

4. For rapidly growing infants, monitoring weekly or twice weekly is recommended.

5. Ketogenic/high-fat diets are frequently employed in individuals who have pyruvate dehydrogenase (PDH) complex deficiency [Patel et al 2012].

6. One was treated with lipid infusions (instead of high-dextrose infusions) during acute episodes [Hong et al 1997, Cerna et al 2001].

Additional therapies used with limited success include the following:

- Thiamine
- Coenzyme Q_{10}
- Lipoic acid
- Riboflavin (though effective in one person with the myopathic form of DLD deficiency)
- Biotin

Table 10. Acute Inpatient Treatment in Individuals with Early-Onset Neonatal Dihydrolipoamide Dehydrogenase Deficiency

Manifestation/Concern	Treatment	Consideration/Other
Underlying precipitating factors	Any precipitating factors (infection, fasting, medications) should be treated/discontinued as soon as possible.	
Metabolic acidosis	• For severe metabolic acidosis (pH <7.20) or if bicarbonate is ≤14 mEq/L, initiate bicarbonate therapy. • A common formula for bicarbonate dose: bicarbonate (mEq) = 0.5 x weight (kg) x [desired bicarbonate - measured bicarbonate] • Administer 1/2 of calculated dose as slow bolus & remaining 1/2 over 24 hrs.	• Metabolic acidosis usually improves w/ generous fluid & calorie support. [1] • Bicarbonate therapy needed for severe metabolic acidosis [2]

Table 10. continued from previous page.

Manifestation/Concern	Treatment	Consideration/Other
Promotion of an anabolic state	D_{10} (half or full-normal saline) w/age-appropriate electrolytes should be started at maintenance rate & adjusted based on presence or absence of ↑ intracranial pressure or hypoglycemia.	• Maintain glucose concentration in normal range. • Intralipids can be added to provide addl calories w/cautious monitoring for acidemia.
Correction of ↑ leucine concentration [3, 4]	• Withhold protein initially for a maximum of 24 hrs to avoid worsening of catabolism. • Then gradually reintroduce protein.	BCAAs should be introduced slowly & followed closely w/frequent plasma amino acid evaluations; see also MSUD.
	Consider renal replacement therapies in clinical settings w/appropriate resources & expertise.	When hemodialysis is used it must be coupled w/effective nutritional mgmt to constrain the catabolic response & prevent recurrent clinical intoxication. [5]
	Total protein intake (enteral + parenteral): 2-3.5 g/kg/day as BCAA-free amino acids	For persons of any age who can tolerate enteral feeding (even if intubated), continuous nasogastric delivery (30-60 mL/hr) of a BCAA-free formula (0.7-1.2 kcal/mL) supplemented w/1% liquid solutions of isoleucine & valine can meet protein goals while providing addl calories.
	Isoleucine & valine supplements (enteral + parenteral): 20-120 mg/kg/day each; titrate to plasma concentrations of 400-800 µmol/L	For parenteral administration, isoleucine & valine are each prepared as separate 1% solutions in normal saline.
Maintain serum osmolality w/in normal reference range (i.e., 275-300 mOsm/kg H_2O). [6]	Establish euvolemia using isotonic sodium chloride solutions.	Overhydration & quickly infused boluses of fluids should be avoided if possible.
	Measure serum osmolality & electrolytes every 6-12 hrs.	Prevent serum osmolality from decreasing >5 mOsm/kg H_2O per day (0.20 mOsm/kg H_2O per hr).
Hypoglycemia	• Start IV fluid. • Maintain blood glucose >100 mg/dL. [7]	• High-dose glucose needed to avoid catabolism • If there is hyperglycemia, start insulin infusion rather than ↓ glucose infusion rate.
Hyperammonemia	• Hyperammonemia improves w/reversal of catabolism. • A high-dose glucose infusion w/insulin infusion is helpful in achieving this goal. • If severe hyperammonemia & altered mental status persist after above measures, extracorporeal toxin removal procedures such as hemodialysis & hemofiltration should be considered.	Although IV sodium benzoate + sodium phenylacetate have been used in such circumstances, their utility in DLD deficiency is doubtful, as most hyperammonemia is accompanied/caused by liver dysfunction, which is responsible for metabolism of nitrogen scavenger medications as well.
Carnitine deficiency	Levocarnitine (IV or PO) 50-100 mg/kg/day divided three times per day should be given during the acute period.	
Lactic acidosis	DCA can be considered & continued.	• If lactate decreases with its introduction • Polyneuropathy is a concern w/long-term use.

Table 10. continued from previous page.

Manifestation/Concern	Treatment	Consideration/Other
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • As seizures typically occur during acute decompensations, ASM may be discontinued when metabolic control is achieved.

ASM = anti-seizure medication; BCAAs = branched-chain amino acids; DCA = dichloroacetate; IV = intravenous; MSUD = maple syrup urine disease; PO = orally

1. Although dextrose infusions may theoretically cause further lactate elevations during acute episodes, provision of dextrose-containing IV fluids is essential for the majority of acutely decompensated individuals. Only one affected individual experienced worsening acidosis with increased dextrose concentrations in the TPN.

2. Note that bicarbonate therapy alone is not sufficient to correct the metabolic acidosis. Correction of metabolic acidosis relies on reversing the catabolic state by providing calorie support from glucose and interlipids.

3. See also Maple Syrup Urine Disease, Management.

4. If there is no evidence of hyperleucinosis, total protein intake can be at the recommended dietary allowance (RDA).

5. Dialysis without simultaneous management of the underlying disturbance of protein turnover is analogous to treating diabetic ketoacidosis with invasive removal of glucose and ketones rather than insulin infusion. In both conditions, effective treatment depends not only on lowering concentrations of pathologic metabolites, but also on controlling the underlying metabolic derangement.

6. To help avoid increased intracranial pressure

7. If provision of dextrose-containing fluids worsens metabolic acidosis, consider decreasing the infusion rate and providing the majority of calories in the form of intralipid.

Hepatic Presentation

Episodes of catabolic stress (e.g., intercurrent illness, surgical procedures, pregnancy) require the assistance/care of a biochemical geneticist.

Table 11. Acute Treatment in Individuals with Acute Liver Injury or Failure Due to Dihydrolipoamide Dehydrogenase Deficiency

Principle/Manifestation	Treatment	Consideration/Other
Underlying precipitating factors	Any precipitating factors (infection, fasting, medications) should be treated/discontinued as soon as possible.	Avoidance of liver-toxic medications (See Agents/Circumstances to Avoid.)
Nutritional support	Dextrose-containing IV fluids (6-8 mg/kg/min) w/ age-appropriate electrolytes &/or frequent feedings	
Metabolic acidosis	Consider correction using sodium bicarbonate (see Table 10).	
Lactic acidosis	DCA can be considered.	If lactate decreases w/its introduction
	Consideration of dialysis	If persistent lactic acidosis & encephalopathy [2]
Coagulopathy	Fresh frozen plasma	

DCA = dichloroacetate; IV = intravenous

1. Brassier et al [2013]

2. Successful in one affected individual

Limited data exist for chronic management of individuals with the primarily hepatic presentation. Between episodes, affected individuals typically return to baseline and do not require treatment beyond the avoidance of fasting, catabolic stressors, and liver-toxic medications.

Myopathic Presentation

At least one affected individual with severe exercise intolerance responded well to riboflavin supplementation (220 mg/day), with resolution of symptoms [Carrozzo et al 2014].

Prevention of Primary Manifestations

No compelling evidence exists for the prevention of acute episodes, despite multiple attempted dietary strategies and medications. The frequency of acute episodes decreases with age in most patients with all forms of DLD deficiency.

- Provide protein intake at or around recommended dietary allowance and titrate based on growth and plasma amino acid values. See Maple Syrup Urine Disease for the recommended intake and target levels of leucine, isoleucine, and valine.
- Supplement with levocarnitine if deficient.

Prevention of Secondary Complications

Dichloroacetate has been associated with the development of peripheral neuropathy; thus, individuals receiving this medication require close monitoring.

Surveillance

Table 12. Recommended Surveillance for Individuals with Dihydrolipoamide Dehydrogenase Deficiency

System/Concern	Evaluation	Frequency/Comment
Feeding	Measurement of growth parameters & eval of nutritional status & safety of oral intake	At each visit
Control of plasma amino acid levels	Full amino acid profile (either from plasma or filter paper)	• For rapidly growing infants, monitoring weekly or 2x weekly • Routinely in older persons [1]
	Visit w/metabolic specialist	At least monthly in infancy
Delayed acquisition of developmental milestones	Monitor developmental milestones. [2, 3]	At each visit or as needed
Hepatomegaly	• Physical exam &/or US to assess size of liver • Blood measurements of liver transaminases & assessment of liver synthetic function	At each visit
Neurologic	Physical exam to evaluate for peripheral neuropathy & EMG if clinically concerned [4]	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Cardiomyopathy	Echocardiogram	At least annually or based on clinical status
Eyes	Ophthalmologic eval	As clinically indicated

OT = occupational therapy; PT = physical therapy; US = ultrasound

1. The frequency of amino acid monitoring varies by age, metabolic stability, compliance, and regional clinical practice and should be guided by a biochemical geneticist in conjunction with a qualified metabolic nutritionist.

2. The Denver Developmental Screening Test II or a comparable tool is useful for monitoring development of infants and young children.

3. School-age children, adolescents, and adults should have neurocognitive testing if indicated by school performance or behavioral problems.

4. In individuals receiving dichloroacetate.

Agents/Circumstances to Avoid

Avoid the following:

- Fasting
- Catabolic stressors
- Extremes of dietary intake until dietary tolerance/stressors are identified
- Liver-toxic medications

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of DLD deficiency and to avoid risk factors that may precipitate an acute event. For at-risk newborn sibs when molecular genetic prenatal testing was not performed: in parallel with newborn screening, either test for the familial *DLD* pathogenic variants or measure plasma lactate, plasma amino acids, and urine organic acids.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Dihydrolipoamide dehydrogenase (DLD) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *DLD* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a *DLD* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If each parent is known to be heterozygous for a *DLD* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with DLD deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *DLD*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DLD* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *DLD* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *DLD* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

No specific resources for Dihydrolipoamide Dehydrogenase Deficiency have been identified by *GeneReviews* staff.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Dihydrolipoamide Dehydrogenase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

DLD	7q31.1	Dihydrolipoyl dehydrogenase, mitochondrial	DLD database	DLD	DLD

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Dihydrolipoamide Dehydrogenase Deficiency (View All in OMIM)

238331	DIHYDROLIPOAMIDE DEHYDROGENASE; DLD
246900	none found

Molecular Pathogenesis

Dihydrolipoamide dehydrogenase (DLD) functions as the E3 subunit in three mitochondrial enzyme complexes (BCKDH, αKGDH, PDH) and the L protein of the glycine cleavage system.

As the E3 subunit, it catalyzes the oxidative regeneration of the lipoic acid covalently bound to the E2 subunit, generating NADH in the process. *DLD* loss-of-function pathogenic variants lead to variable dysfunction of BCKDH, αKGDH, and PDH. The decreased activity of these three enzyme complexes leads to the often severe and variable phenotype seen in DLD deficiency.

To date no person with DLD deficiency has presented with biochemical evidence of glycine cleavage system dysfunction (see Glycine Encephalopathy).

Additionally, multiple *DLD* pathogenic variants have been associated with elevated reactive oxygen species generation [Vaubel et al 2011, Ambrus & Adam-Vizi 2013].

Mechanism of disease causation. DLD deficiency is caused by biallelic pathogenic variants in *DLD* that result in decreased function or loss of function.

Table 13. Notable *DLD* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000108.4 NP_000099.2	c.685G>T	p.Gly229Cys	Founder variant; common in Ashkenazi Jewish population [1] [Scott et al 2010]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Prevalence.

Chapter Notes

Revision History

- 30 September 2021 (sq) Revision: in Treatment of Manifestations: protein intake and hyperleucinosis
- 9 July 2020 (ma) Comprehensive update posted live
- 17 July 2014 (me) Review posted live
- 21 February 2014 (sq) Original submission

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