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**NLM Citation:** Mütze U, Reischl-Hajiabadi A, Kölker S. Classic Isovaleric Acidemia. 2024 Mar 14. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# Classic Isovaleric Acidemia

Synonyms: Classic Isovaleric Aciduria, Isovaleryl-Coenzyme A Dehydrogenase Deficiency

Ulrike Mütze, MD,[1] Anna Reischl-Hajiabadi, MD,[1] and Stefan Kölker, MD[1]

Created: March 14, 2024.

## Summary

### Clinical characteristics

Individuals with clinical manifestations of isovaleric acidemia (IVA) have either classic IVA identified on newborn screening or classic IVA with a later diagnosis due to a missed diagnosis or later onset of clinical manifestations. Classic IVA is characterized by acute metabolic decompensations (vomiting, poor feeding, lethargy, hypotonia, seizures, and a distinct odor of sweaty feet). Acute metabolic decompensations are typically triggered by fasting, (febrile) illness (especially gastroenteritis), or increased protein intake. Clinical deterioration often occurs within hours to days after birth. Additional manifestations of classic IVA include developmental delay, intellectual disability and/or impaired cognition, epilepsy, and movement disorder (tremor, dysmetria, extrapyramidal movements). Early treatment in those identified by newborn screening can significantly reduce morbidity and mortality in individuals with classic IVA.

### Diagnosis/testing

The diagnosis of classic IVA is established in a proband by identification of C5-carnitine metabolites by tandem mass spectrometry and isovalerylglycine (IVG) and 3-hydroxyisovaleric acid (3-HIVA) on analysis of urinary organic acids by gas chromatography-mass spectrometry, or identification of biallelic pathogenic variants in *IVD* by molecular genetic testing.

### Management

*Targeted therapy:* Low-leucine/protein-reduced diet and the supplementation of a leucine-free formula in infants or leucine-free amino acid mixture in older children; carnitine and/or glycine supplementation.

*Supportive care:* Routine daily treatment includes education of affected individuals and caregivers about the natural history, maintenance and emergency treatment, prognosis, and risks of acute encephalopathic crises; emergency treatment letter and MedicAlert®; management of movement disorder per neurologist; physical

**Author Affiliation:** 1 Division of Child Neurology and Metabolic MedicineCenter for Child and Adolescent MedicineUniversity Hospital Heidelberg, Heidelberg, Germany; Email: ulrike.muetze@med.uni-heidelberg.de; Email: anna.reischl-hajiabadi@med.uni-heidelberg.de; Email: stefan.koelker@med.uni-heidelberg.de.

therapy and aggressive rehabilitation therapy for gross motor delay; notify metabolic center prior to planned surgeries; consult metabolic disease specialist with any emergency surgery/procedure.

Emergency outpatient treatment includes carbohydrate supplementation orally or via tube feeding, transient reduction of natural protein intake, elevation of carnitine supplementation, and glycine; antipyretics for fever; antiemetics for vomiting.

Acute inpatient treatment includes stopping protein intake, intravenous glucose, and hydration with normal saline; adjusting treatments for new or evolving neurologic manifestations; consider buffers as needed for life-threatening metabolic acidosis; nitrogen scavengers for hyperammonemia.

*Surveillance:* Quantitative analysis of plasma amino acids at least every three months until age one year, every six months from age one to six years, and annually in those age six years and older; blood gases, albumin, calcium, phosphate, parathyroid hormone, complete blood count, and vitamin $B_{12}$ at least annually in those on a protein-restricted diet; measurement of growth and head circumference at each visit throughout childhood; monitor weight throughout adulthood; monitor developmental milestones at each visit; neuropsychological testing and standardized quality-of-life assessments as needed; assessment of movement disorder at each visit.

*Agents/circumstances to avoid*: Excess of dietary protein or protein malnutrition inducing catabolic state; prolonged fasting; catabolism during illness.

*Evaluation of relatives at risk:* Biochemical or molecular genetic testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of classic IVA.

## Genetic counseling

Classic IVA is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *IVD* 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. Once the *IVD* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

# Diagnosis

## Suggestive Findings

### Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for classic isovaleric acidemia (IVA) is based on the quantification of the first-tier analyte isovalerylcarnitine (as C5-carnitine) in dried blood spots.

C5-carnitine (C5) values above the cutoff reported by the screening laboratory are considered positive and suggest a diagnosis of classic IVA; additional testing of urinary organic acids is required to establish the diagnosis. An algorithm has been proposed for elevated C5 NBS result (see Figure 1).

Additional testing to decrease false positives includes C5 isobar analysis (when available), which can distinguish isovalerylcarnitine from other isobaric carnitines (pivaloylcarnitine, 2-methylbutyrylcarnitine, and N-valerylcarnitine) that cannot be distinguished by tandem mass spectrometry [Murko et al 2022]. Such testing can be performed in regions with increased use of pivalic acid-containing antibiotics (taken by mother and child) and pivalic acid-containing skin cream derived from pivaloylcarnitine. Analysis of urinary organic acids (see Establishing the Diagnosis) can also exclude false positive results on tandem mass spectrometry due to pivaloylcarnitine, or due to unrelated metabolites secondary to 2-methylbutyrylglycinuria [AWMF 2019] (see Differential Diagnosis).

The majority of individuals with classic IVA present acutely with life-threatening metabolic decompensation during the first two weeks of life. Therefore, infants with C5 >4 µmol/L on the first NBS sample that do not have access to C5 isobar analysis should begin the following medical interventions while urine organic acids are performed to establish the diagnosis of classic IVA [Mütze et al 2021, Mütze et al 2023b]:

- Promotion of catabolism and avoidance of fasting
- Clinical assessment by a pediatrician or at a pediatric metabolic center including measurement of ammonia and blood gases
- Consideration of carnitine supplementation (50-100 mg/kg/day orally or intravenously)

### Scenario 2: Symptomatic Individual

A symptomatic individual can have delayed diagnosis of classic IVA or untreated classic IVA due to any of the following: NBS not performed, false negative NBS result, or caregivers not adherent to recommended treatment following a positive NBS result. Supportive – but nonspecific – can include the following clinical, preliminary laboratory, brain MRI, and family history findings.

**Clinical findings** [Schiff et al 2022]

- Acute metabolic decompensation (vomiting, altered mental status, reduced consciousness or coma, lethargy). An odor of sweaty feet can be present during these episodes.
- Feeding difficulties and episodic vomiting
- Hypotonia
- Developmental delay / intellectual disability
- Movement disorder (tremor, dysmetria, extrapyramidal movements)
- Ataxia
- Seizures

**Preliminary laboratory findings** [Schiff et al 2022]

- Metabolic acidosis with elevated anion gap
- Ketonuria
- Hyperammonemia
- Hematologic abnormalities (e.g., bone marrow suppression resulting in leukopenia, thrombocytopenia, and/or anemia)

**Brain MRI findings.** In contrast to other organic acidurias (e.g., propionic acidemia, methylmalonic acidemia, and glutaric acidemia type 1) there are no characteristic MRI findings. During metabolic decompensations intraventricular and/or cerebellar hemorrhage and edema are possible [Schiff et al 2022].

**Family history** is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of classic IVA in a proband with suggestive biochemical and/or clinical findings **is established** by identification of:

- C5-carnitine (C5) metabolites, isovalerylglycine (IVG), and 3-hydroxyisovaleric acid (3-HIVA) on analysis of urinary organic acids by gas chromatography-mass spectrometry [Tavares de Almeida & Ribes 2022];

  **OR**

- Biallelic pathogenic (or likely pathogenic) variants in *IVD* by molecular genetic testing (see Table 2).

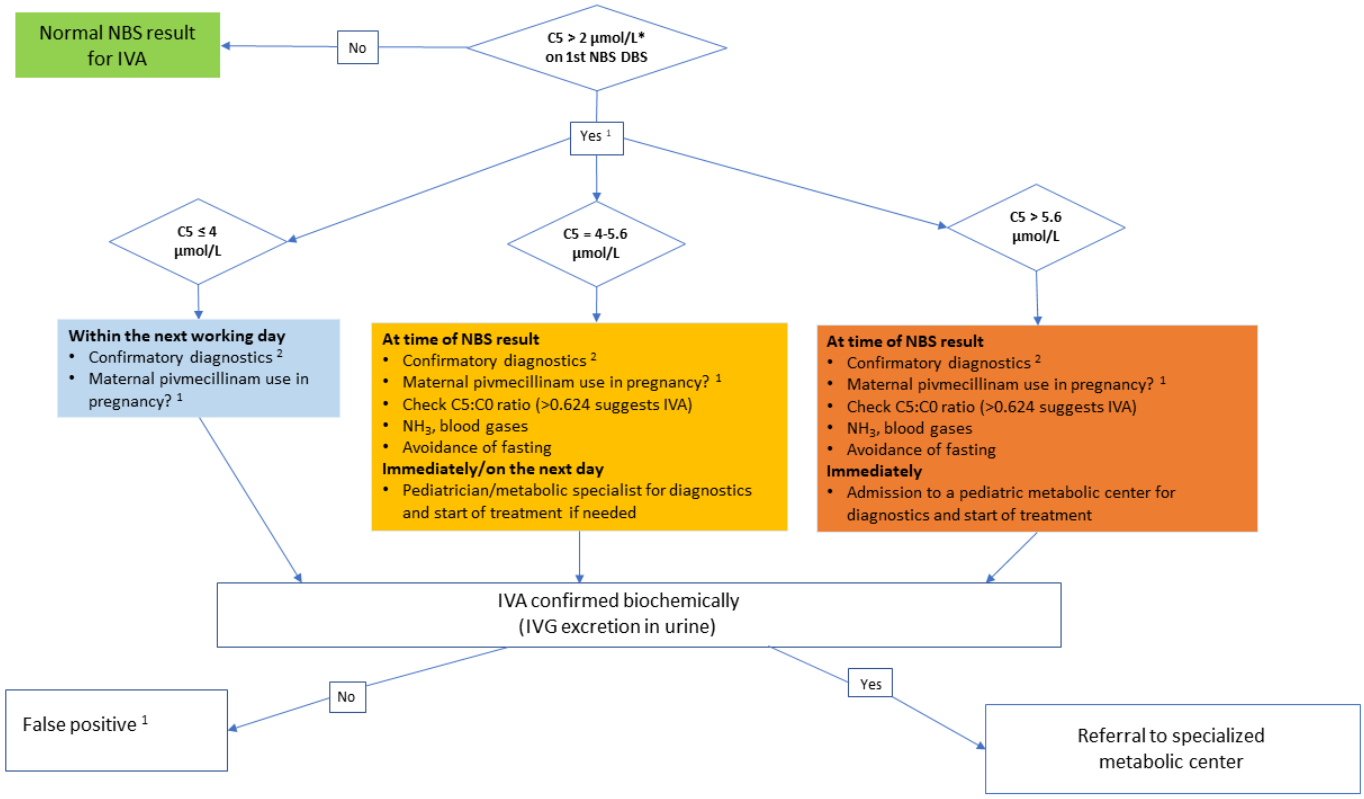


**Figure 1.** Proposed algorithm following newborn screening (NBS) result suggestive of isovaleric acidemia (IVA)

C0 = free carnitine; C5 = C5-carnitine; DBS = dried blood spot; IVA = isovaleric acidemia; IVG = isovalerylglycine; NBS = newborn screening; $NH_3$ = ammonia

* Cutoff values are provided from the Heidelberg University Hospital laboratory to assist the reader in comparing the data of their own laboratories. Due to differences between NBS programs worldwide, this algorithm should be adapted to the respective national NBS organization structures and cutoffs prior to use. Statistically derived absolute cutoffs should be used with caution.

1. False positive results on tandem mass spectrometry can be caused by exposure to pivaloylcarnitine, a derivative of pivalic acid-containing antibiotics (taken by mother and child) and pivalic acid-containing skin cream. If available without time loss, a second-tier using ultra-performance liquid chromatography-tandem mass spectrometry to analyze C5 isobars significantly reduces such false positives [Murko et al 2022]. Postanalytic tools and machine learning methods can also reduce false positives [Hall et al 2014, Mütze et al 2023b, Zaunseder et al 2023].

2. Confirmatory diagnostics consist of a second NBS dried blood sample and the analysis of urine organic acids to confirm or exclude classic IVA.

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Note: (1) Some *IVD* variants are known to be associated with attenuated IVA (e.g., p.Ala311Val; see Genetically Related Disorders). Attenuated IVA should be distinguished from classic IVA because infants with classic IVA need immediate and continuous treatment and infants with attenuated IVA do not need aggressive treatment and should be protected from overtreatment [Mütze et al 2021]. Of infants identified on NBS in Germany, 80% had attenuated IVA. Biochemical findings (e.g., only mild elevations in metabolites) may be helpful to distinguish classic IVA from attenuated IVA [Mütze et al 2023b]. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (3) Identification of biallelic *IVD* variants of

uncertain significance (or of one known *IVD* pathogenic variant and one *IVD* variant of uncertain significance) does not establish or rule out the diagnosis.

### Molecular Genetic Testing

**Single-gene testing.** Sequence analysis of *IVD* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: 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 next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**Table 2.** Molecular Genetic Testing Used in Classic Isovaleric Acidemia

| Gene [1] | Method | Proportion of Pathogenic Variants [2] Identified by Method |
|---|---|---|
| *IVD* | Sequence analysis [3] | >90% [4] |
| | Gene-targeted deletion/duplication analysis [5] | <10% [4] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

# Clinical Characteristics

## Clinical Description

The clinical spectrum of classic isovaleric acidemia (IVA) is broad and differs according to age of onset and severity of disease. Classic IVA is characterized by early onset of acute metabolic decompensations (vomiting, poor feeding, lethargy, hypotonia, seizures, and a distinct odor of sweaty feet), epilepsy, developmental delay, intellectual disability and/or impaired cognition, and movement disorder. Individuals with classic IVA (not identified on newborn screening) may have delayed diagnosis if acute metabolic decompensations occur later in childhood and/or they have nonspecific poor weight gain, growth deficiency, and developmental delay.

**Table 3.** Select Features of Classic Isovaleric Acidemia

| Feature | % of Persons w/Feature | | |
|---|---|---|---|
| | Identified by NBS [1] | Not identified by NBS | |
| | | Early onset w/prompt diagnosis | Delayed diagnosis (missed diagnosis or later onset) |
| Acute metabolic decompensations | 70% [2] | 90%-100% [3] | 80% [4] |
| Seizures | 15% [1] | Prevalent [5] | Prevalent [5] |
| Speech/language delay | 15%-20% [1, 6] | 25% [4] | Prevalent [5] |
| Gross/fine motor delay | 5%-16% [1, 6] | Prevalent [4, 5] | Prevalent [5] |
| Intellectual disability / impaired cognition | 10% [1] | 15%-18% [4] | 55%-56% [4] |

*Table 3. continued from previous page.*

| Feature | % of Persons w/Feature | | |
|---|---|---|---|
| | Identified by NBS [1] | Not identified by NBS | |
| | | Early onset w/prompt diagnosis | Delayed diagnosis (missed diagnosis or later onset) |
| Muscular hypotonia | 5% [1] | Prevalent [4, 5] | Prevalent [5] |
| Movement disorder | 15% [1] | Prevalent [4, 5] | Prevalent [5] |
| Infantile mortality | 0% [1] | 33% [4] | 3% [4, 7] |

NBS = newborn screening
*1.* Mütze et al [2021]
*2.* In those with classic IVA identified on newborn screening, 50% of decompensations occur in the neonatal period [Mütze et al 2021].
*3.* In those with classic IVA not identified on newborn screening, most present with metabolic decompensation [Grünert et al 2012, Kölker et al 2015b].
*4.* Grünert et al [2012]
*5.* Kölker et al [2015b]
*6.* Heringer et al [2016]
*7.* This frequency is quite likely to be underestimated, as a relevant number of infants and children might have died without correct diagnosis.

**Acute metabolic decompensations** in individuals with classic IVA can occur either early in the neonatal period or later in life. These life-threatening episodes are typically triggered by fasting, (febrile) illness (especially gastroenteritis [Grünert et al 2012]), or increased protein intake. During metabolic decompensation, individuals may exhibit various manifestations reflecting metabolic derangement (partially compensated metabolic acidosis, elevated lactate, ketosis, hyperammonemia), including vomiting, poor feeding, lethargy, hypotonia, seizures, and a distinct odor of sweaty feet [Dionisi-Vici et al 2006].

- **Diagnosis through newborn screening (NBS) and early treatment** can reduce the incidence of metabolic decompensations in individuals with classic IVA, although neonates can present with metabolic decompensation before NBS results are available (see Figure 2) [Mütze et al 2021]. Recurrent decompensations are less frequent in individuals identified through NBS compared to those diagnosed based on symptoms alone, and the frequency of decompensations tends to decrease with age, with no instances reported after early adolescence [Grünert et al 2012, Mütze et al 2021].
- Individuals with **classic IVA not identified by NBS** usually develop the first manifestations of acute metabolic decompensation after a short symptom-free period after birth. Clinical deterioration often occurs within hours to days after birth with feeding refusal, recurrent vomiting, progressive weight loss, generalized hypotonia, abnormal posturing, and abnormal movements, and a distinctive odor of sweaty feet can be present. Laboratory abnormalities include severe metabolic acidosis with elevated anion gap, elevated lactate, ketosis, and hyperammonemia [Dionisi-Vici et al 2006, Kölker et al 2015a, Kölker et al 2015b]. Subsequently, individuals may exhibit lethargy, seizures, and coma, leading to death within a few days or resulting in severe neurologic damage if diagnosis of classic IVA is not identified and/or treatment is not started.

  Metabolic decompensations can occur any time throughout childhood in individuals with classic IVA (regardless of age of diagnosis). Metabolic decompensations did not occur after early adolescence in 21 children with classic IVA [Grünert et al 2012]. However, some individuals have had acute metabolic decompensations in adulthood [Schlune et al 2018, Tuncel et al 2018].

**Seizures** have been reported in individuals with classic IVA detected through NBS [Mütze et al 2021] and those diagnosed later [Kölker et al 2015b]. However, data on the proportion of individuals affected, age of onset, seizure types, seizure frequency, and EEG findings are limited. One child, age five months, was described with

infantile spasms and hypsarrhythmia observed on EEG during a metabolic decompensation [Sezer & Balci 2016].

**Developmental delay.** Delays in gross and fine motor development and speech and language have been reported in individuals with classic IVA detected through NBS, particularly those with neonatal metabolic decompensation despite early diagnosis by NBS [Mütze et al 2021]. However, in individuals with classic IVA diagnosed after the onset of symptoms, developmental disorders affecting motor and cognitive functions are more prevalent, particularly in those with a late diagnosis (>50% had developmental delay) [Grünert et al 2012]. Delayed motor development is often accompanied by muscular hypotonia and movement disorders.

**Intellectual disability / impaired cognition.** In one cohort, individuals with classic IVA identified on NBS had lower IQ levels than the general population (mean IQ: 91±10), and IQ levels were even lower in those who had experienced severe neonatal metabolic decompensation [Mütze et al 2021]. In another cohort of 16 affected individuals with classic IVA, cognitive function was within the normal range for those identified through NBS and clinically diagnosed individuals [Couce et al 2017].

Among individuals with a later diagnosis, approximately 60% were reported to have normal neurocognitive outcomes. Learning disabilities were observed in approximately one quarter of affected individuals. Severe cognitive dysfunction was reported in 5% of individuals.

Early diagnosis and treatment in those who survive the initial metabolic decompensation tends to result in better neurocognitive outcomes [Grünert et al 2012]. A multicenter study showed that early diagnosis and treatment significantly impact the clinical and neurocognitive outcomes of individuals with classic IVA [Heringer et al 2016].

**Movement disorder** (tremor, dysmetria, extrapyramidal movements). The onset of a movement disorder usually occurs early in the disease course, particularly in infants and children with recurrent acute metabolic decompensations prior to diagnosis and the start of treatment. Depending on the extent of brain damage, the severity of the movement disorder can vary; however, it is mostly mild to moderate. Since the movement disorder is the neurologic sequelae of preceding brain damage, the movement disorder is stable unless brain damage is aggravated through recurrent severe metabolic decompensations.

**Behavioral problems.** No behavioral abnormalities have been reported in cohorts of individuals with classic IVA identified through NBS [Heringer et al 2016, Schlune et al 2018, Mütze et al 2021]. Although data is limited, behavioral problems such as attention-deficit/hyperactivity disorder have been reported in individuals with classic IVA not identified on NBS [Hertecant et al 2012]. These issues may arise during episodes of metabolic derangement or due to the impact on the central nervous system.

**Hematologic manifestations** have not been reported in individuals with classic IVA detected through NBS [Vockley & Ensenauer 2006, Schlune et al 2018, Mütze et al 2021], unlike in other forms of organic acidemias, particularly methymalonic acidemia and propionic acidemia. Pancytopenia as well as isolated neutropenia, thrombocytopenia, or anemia can occur as a result of bone marrow suppression during acute metabolic decompensations. However, these hematologic abnormalities have not been consistently reported in cohorts in the literature [Vockley & Ensenauer 2006, Kölker et al 2015b].

**Pancreatitis** has not been reported in individuals with classic IVA detected through NBS [Kölker et al 2015a, Kölker et al 2015b, Couce et al 2017, Schlune et al 2018, Mütze et al 2021]. Pancreatitis has been reported in some individuals with late-onset IVA and in some with early onset but delayed diagnosis and may complicate the disease course [Dionisi-Vici et al 2006, Kölker et al 2015a, Kölker et al 2015b, Schlune et al 2018].

**Growth.** Information regarding growth in individuals with classic IVA is limited; growth deficiency has not been consistently reported and may vary among affected individuals. Feeding problems and gastrointestinal

manifestations (e.g., vomiting) do not appear to cause growth deficiency in individuals with classic IVA [Kölker et al 2015b], but long-term protein restriction might negatively impact growth [Mütze et al 2023a].

**Other features**

- Fanconi syndrome (1 individual) [Vockley & Ensenauer 2006]
- Cardiac arrhythmias during general and local anesthesia (1 individual) [Vockley & Ensenauer 2006]
- Abnormalities of the globus pallidus (1 individual) [Vockley & Ensenauer 2006]
- Optic nerve atrophy (1 individual) [Kölker et al 2015b]

**Prognosis.** Early treatment in those identified by NBS can significantly reduce mortality in individuals with classic IVA [Mütze et al 2021]. Although there is limited data on older individuals with classic IVA detected through NBS, there is no apparent disease progression or evidence of multisystem organ dysfunction, which is frequently observed in individuals with other organic acidemias such as propionic acidemia and methylmalonic acidemia, suggesting a more favorable prognosis in individuals with classic IVA [Tuncel et al 2018].

Untreated individuals with classic IVA can develop metabolic decompensation resulting in cerebral edema and hemorrhage, coma, and death [Vockley & Ensenauer 2006]. Mortality is high in neonates during initial metabolic decompensation (about 30%). However, infants who survive benefit from prompt initiation of treatment, resulting in better neurocognitive outcomes compared to individuals with delayed diagnosis and treatment [Grünert et al 2012].

Metabolic decompensations rarely occur in individuals with classic IVA after adolescence, with only a few reports of metabolic decompensation in adulthood [Grünert et al 2012, Tuncel et al 2018].

**Classic IVA with delayed diagnosis.** Before the implementation of tandem mass spectrometry-based NBS that included the diagnosis of IVA, individuals with classic IVA were diagnosed at a median age of four years, most often following an acute metabolic crisis or in an individual with unexplained developmental delay [Grünert et al 2012]. However, the majority of these individuals had preceding acute metabolic crises as neonates. Similarly, early literature originally suggested two forms of IVA, a neonatal group presenting with acute life-threatening encephalopathy and a second group presenting in childhood with nonspecific poor feeding with selective refusal of protein-rich foods, recurrent vomiting, poor weight gain, growth deficiency, intermittent ataxia, abnormal behavior, and/or neurodevelopmental delay [Tanaka 1990]. Individuals who survived the first neonatal episode, however, were indistinguishable from those presenting in childhood, suggesting that there is a continuous phenotypic disease spectrum [Vockley & Ensenauer 2006], and delayed diagnosis may be due to missed diagnosis or later onset.

## Genotype-Phenotype Correlations

Limited information is available regarding genotype-phenotype correlations [Vockley & Ensenauer 2006, Mütze et al 2023b].

The pathogenic variant p.Ala311Val is particularly common in individuals identified through NBS and is associated with attenuated IVA in individuals who are homozygous or compound heterozygous for this variant (see Genetically Related Disorders). These individuals exhibit only mild elevations in metabolites and have an asymptomatic disease course [Ensenauer et al 2004, Mütze et al 2021, Mütze et al 2023b]. Additional *IVD* pathogenic variants can also result in attenuated IVA [Mütze et al 2021].

## Nomenclature

**Classic isovaleric acidemia/aciduria** refers to the presence of elevated levels of isovaleric acid in the blood/urine.

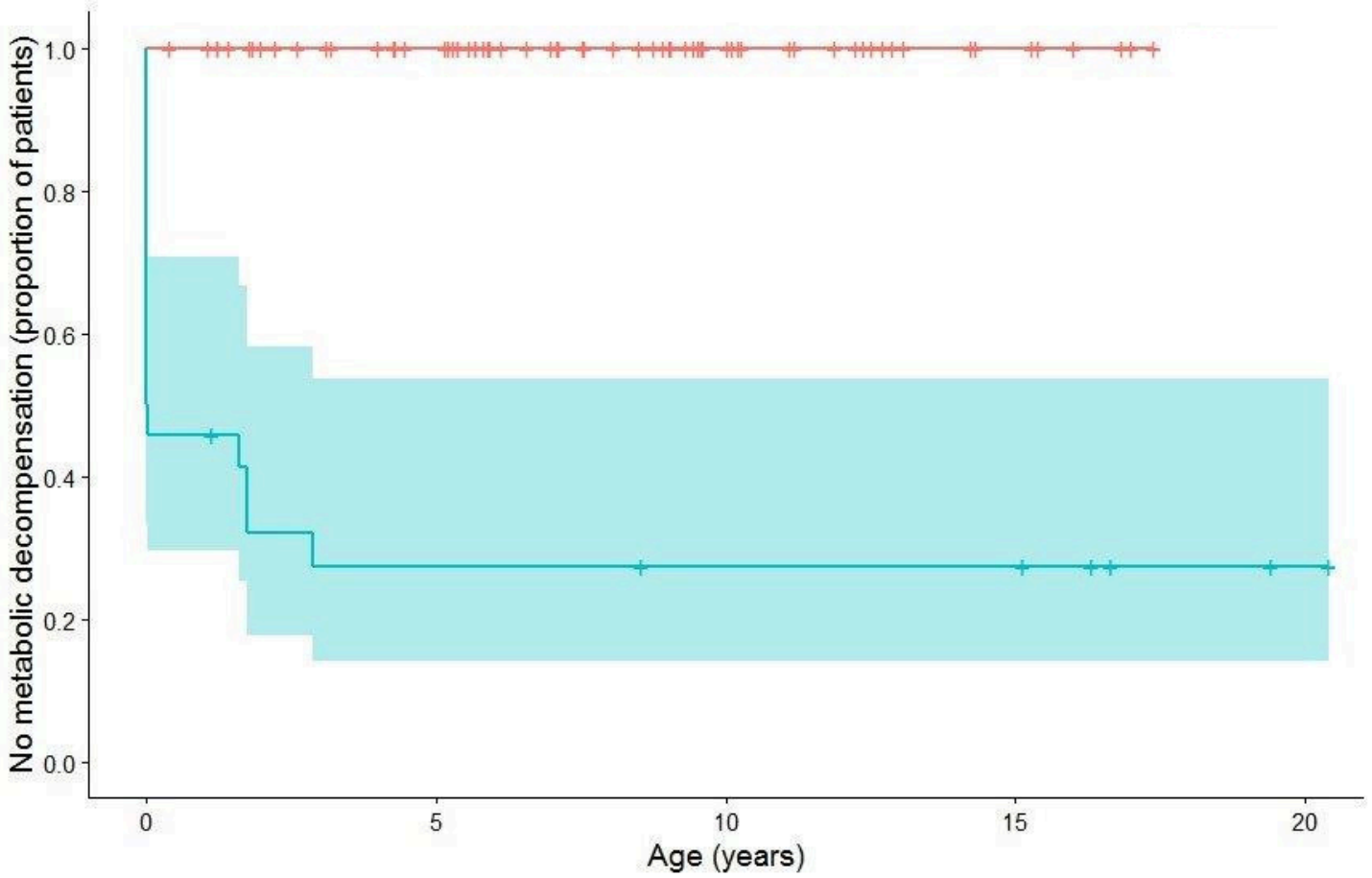


**Figure 2.** Age at first metabolic decompensation

Kaplan-Meier analysis of age at onset of first metabolic decompensation. Individuals with attenuated IVA (red; n = 67) experienced no metabolic decompensations (see Genetically Related Disorders), whereas the majority of individuals with classic IVA (turquoise; n = 24) had at least one metabolic decompensation. Vertical lines indicate censored data; color-shaded areas indicate the 95% confidence intervals.

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**Isovaleryl-coenzyme A dehydrogenase deficiency** refers to inherited deficiency of the mitochondrial FAD-dependent enzyme isovaleryl-coenzyme A dehydrogenase resulting in isovaleric acidemia.

## Prevalence

Prevalence of classic IVA is 1:100,000 newborns [Moorthie et al 2014, Mütze et al 2021]. There are no known founder variants or populations with high disease prevalence.

# Genetically Related (Allelic) Disorders

**Attenuated IVA** (also known as "attenuated disease variant"; formerly referred to as "mild IVA"). Individuals with biallelic *IVD* variants can present with mild elevations in C5-carnitine (<~6 µmol/L on NBS) and absence of typical clinical manifestations of classic IVA (acute metabolic decompensations, seizures, motor delay, hypotonia, and movement disorder). This phenotype occurs predominantly (>80%) in homozygous or compound heterozygous individuals with the common *IVD* missense variant NM_002225.5:c.932C>T (p.Ala311Val). These individuals have normal cognitive function (mean IQ: 105±16), even without dietary treatment and/or medication [Ensenauer et al 2004, Mütze et al 2021, Mütze et al 2023b]. Infants with

attenuated IVA do not need aggressive treatment and should be protected from overtreatment [Mütze et al 2021]. These individuals can follow a normal diet without any restrictions with avoidance of prolonged and/or excessive fasting. In those with severely increased or prolonged catabolism, treatment includes intravenous glucose, rehydration with normal saline, and consideration of transient use of carnitine.

# Differential Diagnosis

## Scenario 1: Abnormal Newborn Screening (NBS) Result

**Table 4a.** Genes of Interest in the Differential Diagnosis of an Infant with NBS Results and/or Other Laboratory Findings Suggestive of Classic Isovaleric Acidemia

| Gene(s) | Disorder | MOI | Laboratory Findings | Clinical Findings |
|---|---|---|---|---|
| *ACADSB* | Short/branched-chain acyl-CoA dehydrogenase deficiency (2-methylbutyrylglycinuria) (OMIM 610006) | AR | ↑ C5 [1] | • DD<br>• Seizures<br>• Autism<br>• Majority of persons remain asymptomatic |
| *ETFA*<br>*ETFB*<br>*ETFDH* | Multiple acyl-CoA dehydrogenase deficiency (MADD, glutaric aciduria II) | AR | • ↑ C5<br>• Metabolic acidosis<br>• Hypoglycemia [1] | • Muscular hypotonia & weakness<br>• Liver dysfunction<br>• Cardiomyopathy |

C5 = C5-carnitine; AR = autosomal recessive; CoA = coenzyme A; DD = developmental delay; MOI = mode of inheritance
*1.* Schlune et al [2018]

Of note, pivaloylcarnitine, a derivate of pivalic acid-containing antibiotics (taken by mother and child) and pivalic acid-containing skin cream, can cause a false positive newborn screening (NBS) for isovaleric acidemia (IVA), as pivaloylcarnitine is isobaric for isovalerylcarnitine and can also cause elevated C5-carnitine values on tandem mass spectrometry of dried blood spots [Schlune et al 2018, Murko et al 2022]. False positive results on tandem mass spectrometry due to pivaloylcarnitine can be excluded by C5 isobar analysis (where available) [Murko et al 2022] or analysis of urinary organic acids.

## Scenario 2: Symptomatic Individual

**Table 4b.** Genes of Interest in the Differential Diagnosis of a Symptomatic Individual with Findings Suggestive of Late-Onset or Untreated Infantile-Onset Classic Isovaleric Acidemia

| Gene(s) | Disorder | MOI | Laboratory Findings | Clinical Findings |
|---|---|---|---|---|
| *GCDH* | Glutaric acidemia type 1 | AR | Metabolic acidosis [1, 2] | • Acute encephalopathic crises<br>• Macrocephaly<br>• Seizures |
| *MCEE*<br>*MMAA*<br>*MMAB*<br>*MMADHC*<br>*MMUT* | Isolated methylmalonic acidemia | AR | • Metabolic acidosis<br>• Hyperammonemia<br>• Methylmalonic acid in urine<br>• Propionylcarnitine on acylcarnitine analysis [1, 3] | • Metabolic decompensations<br>• Cardiomyopathy<br>• Kidney failure<br>• Pancreatitis |
| *PCCA*<br>*PCCB* | Propionic acidemia | AR | • Metabolic acidosis<br>• Hyperammonemia<br>• 3-hydroxy-propionic acid & 2-methylcitrate in urine<br>• Propionylcarnitine on acylcarnitine analysis [1, 3] | |
| *ARG1* | Arginase deficiency | AR | • Hyperammonemia<br>• ↑ arginine in plasma<br>• ↑ liver enzymes [1, 4] | • Altered level of consciousness<br>• Encephalopathy<br>• Seizures |

*Table 4b. continued from previous page.*

| Gene(s) | Disorder | MOI | Laboratory Findings | Clinical Findings |
|---|---|---|---|---|
| *ASL* | Argininosuccinate lyase deficiency | AR | • Hyperammonemia<br>• Argininosuccinic acid in plasma or urine<br>• ↑ liver enzymes [1, 4] | • Vomiting<br>• Cognitive impairment<br>• Hepatomegaly |
| *ASS1* | Citrullinemia type I | AR | • Hyperammonemia<br>• ↑ citrulline in plasma<br>• ↑ liver enzymes [1, 4] | |
| *CPS1* | Carbamoylphosphate synthetase I deficiency (See Urea Cycle Disorders Overview.) | AR | • Hyperammonemia<br>• Low citrulline in plasma<br>• Normal/low orotic acid in urine<br>• ↑ liver enzymes [1, 4] | |
| *OTC* | Ornithine transcarbamylase deficiency | XL | • Hyperammonemia<br>• Low citrulline in plasma<br>• ↑ orotic acid in urine<br>• ↑ liver enzymes [1, 4] | |
| *NAGS* | N-acetylglutamate synthase deficiency (See Urea Cycle Disorders Overview.) | AR | • Hyperammonemia<br>• Low citrulline in plasma<br>• Normal/low orotic acid in urine<br>• ↑ liver enzymes [1, 4] | |
| *SLC25A13* | Citrin deficiency | AR | • Hyperammonemia<br>• ↑ citrulline, arginine, methionine, threonine, tyrosine, & lysine in plasma<br>• ↑ liver enzymes [1, 4] | |
| *SLC25A15* | Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome | AR | • Hyperammonemia<br>• ↑ homocitrulline in urine<br>• ↑ liver enzymes [1, 4] | |

AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

*1.* Kölker et al [2015a], Kölker et al [2015b]
*2.* Boy et al [2023]
*3.* Forny et al [2021]
*4.* Häberle et al [2019]

# Management

When classic isovaleric acidemia (IVA) is suspected during the diagnostic evaluation, that is, because of increased C5-carnitine concentrations in dried blood spots (acylcarnitine profile) or isovalerylglycine in urine (urine organic acids), metabolic 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 classic IVA, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Classic Isovaleric Acidemia: Recommended Evaluations Following Initial Diagnosis

| Evaluation | Comment |
|---|---|
| **Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian** [1] | • Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended)<br>• Consideration of short hospitalization at center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises) |
| **Nutrition / Feeding assessment** | In symptomatic children w/feeding problems, need for tube feeding should be carefully evaluated by metabolic specialist & nutritional specialist. |
| **Consultation w/neurologist** | In symptomatic persons, neurologic phenotype should be carefully assessed by child neurologist (in children & adolescents) or neurologist (in adults) |
| **Developmental assessment** | Consider referral to developmental pediatrician. |
| **Consultation w/psychologist &/or social worker** | To ensure understanding of diagnosis, assess parental / affected person's coping skills & resources, and provide sociolegal advice |
| **Consultation w/physical therapist, occupational therapist, & speech therapist** | To ensure long-term benefit from treatment & to guide support of development (if necessary) |
| **Genetic counseling by genetics professionals** [2] | To inform affected persons & their families re nature, MOI, & implications of classic IVA to facilitate medical & personal decision making |

IVA = isovaleric acidemia; MOI = mode of inheritance

*1.* After a new diagnosis of classic IVA in a child, the closest hospital and local pediatrician should also be informed.

*2.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

All children with classic IVA require supervision of a specialist metabolic dietitian with experience in managing the diet recommended for those with classic IVA. The main principles of treatment are aimed at reducing leucine and enhancing physiologic detoxification of isovaleryl-coenzyme A, which is considered the main endogenous toxin of individuals with classic IVA.

### Targeted Therapy

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

**Low-leucine diet in infants**

- Reduction of total natural protein (leucine) intake via breast milk or conventional formula
- Leucine-free formulas to provide adequate supply of essential amino acids with minerals, trace elements, and vitamins
- Diet must balance reduced leucine intake while maintaining sufficient intake of essential nutrients.
- Total protein prescription is according to safe levels of protein recommended by the World Health Organization / Food and Agriculture Organization of the United Nations / United Nations University (WHO/FAO/UNU)
- Natural protein intake for individuals with classic IVA is adjusted to the individual leucine tolerance. For the first year of life this accounts for a natural protein intake of about 0.8-1 g/kg/day plus protein from leucine-free formulas (1-1.5 g/kg/day).

**Pharmacologic detoxification**

- Conjugation of isovaleryl-coenzyme A using carnitine or combined carnitine and glycine
- Carnitine supplementation dose: 50-100 mg/kg/day
- Glycine supplementation dose: 150 mg/kg/day

## Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This involves multidisciplinary care by specialists in relevant fields for routine daily treatment (see Table 6a), emergency outpatient treatment (see Table 6b), and acute inpatient treatment (see Table 6c).

**Table 6a.** Classic Isovaleric Acidemia: Routine Daily Treatment

| Principle/Manifestation | Treatment | Considerations/Other |
|---|---|---|
| **General** | Intense & ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises | |
| **Nutrition / Dietary management** | Low-leucine diet **in infants** (See Targeted Therapy.) | |
| | After being given prescribed quantities of leucine-free formula, infants can breastfeed on demand. | • Breastfeeding should be encouraged.<br>• Leucine content in breast milk is 130 mg per 100 mL.<br>• Daily leucine intake can be calculated when breast milk is the only natural protein source & breast milk intake is calculated & stable. |
| | • Protein-controlled diet **in adolescents & adults** to avoid excess protein<br>• Adequate supplies of specialized dietary products should always be maintained at home. | After school age the dietary mgmt is usually relaxed. With increasing age, the risk of acute metabolic decompensations declines. Metabolic decompensations are usually not present after adolescence (except for a few reported instances). The natural protein intake can be adjusted to the WHO/FAO/UNU safe levels of protein to avoid protein malnutrition. |
| **Acute metabolic decompensation** | • Treatment protocols & provision of emergency letters or cards to include guidance for care in the event of illness while on holiday/vacation<br>• MedicAlert® bracelets/pendants or car seat stickers | • Written protocols for maintenance & emergency treatment should be provided to parents, primary care providers / pediatricians, teachers, & school staff. [1, 2]<br>• Emergency letters/cards should be provided summarizing key information & principles of emergency treatment for classic IVA & containing contact information for primary treating metabolic center.<br>• For any planned travel or vacations, consider contacting a center of expertise near the destination prior to travel dates. |
| **Movement disorders** | Referral to neurologist for ongoing mgmt | |
| **Gross motor delay** | • Physical therapy<br>• Aggressive rehab therapy | |

*Table 6a. continued from previous page.*

| Principle/Manifestation | Treatment | Considerations/Other |
|---|---|---|
| **Surgery or procedure (including dental procedures)** | • Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/surgeons & anesthesiologists.<br>• Emergency surgeries/procedures require planning input from physicians w/ expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt). | Consider placing a "flag" in the affected person's medical record such that all care providers are aware of the diagnosis & the need to solicit opinions & guidance from designated metabolic specialists in the setting of certain procedures. |

Based on British Inherited Metabolic Diseases Group, European registry and network for Intoxication type Metabolic Diseases (E-IMD), Pinto et al [2017], Mütze et al [2021], Schiff et al [2022]
IVA = isovaleric acidemia; WHO/FAO/UNU = World Health Organization / Food and Agriculture Organization of the United Nations / United Nations University
*1.* Essential information including written treatment protocols should be provided before inpatient emergency treatment might be necessary.
*2.* Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5 °C; (2) vomiting/diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic manifestations occur.

**Table 6b.** Classic Isovaleric Acidemia: Emergency Outpatient Treatment

| Manifestation | Treatment | Consideration/Other |
|---|---|---|
| **Mildly increased catabolism** [1] | • Carbohydrate supplementation orally or via tube feeding [2]<br>• Transient reduction of natural protein intake [3]<br>• Increase carnitine supplementation (up to 200 mg/kg/day)<br>• Glycine supplementation (up to 300 mg/kg/day) | • Trial of outpatient treatment at home for up to 12 hours<br>• Reassessment (~every 2 hours) for clinical changes [4] |
| **Fever** | Administration of antipyretics (acetaminophen, ibuprofen) if temperature rises >38.5 °C | |
| **Occasional vomiting** | Antiemetics [5] | |

Based on British Inherited Metabolic Diseases Group, European registry and network for Intoxication type Metabolic Diseases (E-IMD), Pinto et al [2017], Schiff et al [2022]
*1.* Fever <38.5 °C (101 °F); enteral or gastrostomy tube feeding is tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)
*2.* Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting, with some centers recommending frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.
*3.* Some centers advocate additional steps such as reducing natural protein intake to zero or to 50% of the normal prescribed regimen for short periods (<24 hours) in the outpatient setting during intercurrent illness.
*4.* Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features discussed with the designated center of expertise for inherited metabolic diseases
*5.* Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to the hospital.

**Table 6c.** Classic Isovaleric Acidemia: Acute Inpatient Treatment

| Manifestation | Treatment | Consideration/Other |
|---|---|---|
| **Increased catabolism (due to fever, perioperative/peri-interventional fasting periods, repeated vomiting/diarrhea)** | • Transient stop of protein intake<br>• Intravenous glucose to restore anabolism<br>• Normal saline for rehydration | • Do not stop protein for >24 hours to avoid protein catabolism.<br>• Glucose should be administered according to age, aiming to cover the gluconeogenesis rate of the liver (e.g., 12-15 g/kg/day in newborns).<br>• Fluid intake is adjusted to age-dependent demands & should consider additional losses (e.g., vomiting, diarrhea). |
| **New or evolving neurologic manifestations** | Adjust treatment after careful exam of secondary causes & following neurologic consultation & cranial MRI. | |
| **Metabolic acidosis** | Consider use of buffers (in case of life-threatening acidosis). | |
| **Hyperammonemia** | Nitrogen scavengers | Sodium benzoate: starting dose 250 mg/kg/day intravenously;, consider intravenous bolus or dose escalation in case of life-threatening hyperammonemia (usually rare). |

British Inherited Metabolic Diseases Group, European registry and network for Intoxication type Metabolic Diseases (E-IMD), Pinto et al [2017], Schiff et al [2022]

## Surveillance

In addition to regular evaluations by a metabolic specialist and metabolic dietician, the evaluations summarized in Table 7 are recommended to monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations.

**Table 7.** Classic Isovaleric Acidemia: Recommended Surveillance

| Manifestation | Evaluation | Frequency/Comment |
|---|---|---|
| **Nutrition/ Growth** | Quantitative analysis of plasma amino acids (ideally sent after a 3-hour protein fast) | • At least every 3 months until age 1 year<br>• Every 6 months from ages 1-6 years<br>• Annually age ≥6 years |
| | Laboratory testing (blood gases, albumin, calcium, phosphate, parathyroid hormone, complete blood count, vitamin $B_{12}$) | At least annually in those on protein-restricted diet |
| | Measurement of growth & head circumference | At each visit throughout childhood; continue to monitor weight throughout adulthood |
| **Development** | Monitor developmental milestones. | At each visit |
| | • Neuropsychological testing using age-appropriate standardized assessments<br>• Standardized quality-of-life assessment tools for affected persons & parents/caregivers | As needed |
| **Movement disorder** | Assessment for clinical manifestations of movement disorders, severity, & response to treatment (physical therapy & pharmacologic interventions) | At each visit |

## Agents/Circumstances to Avoid

Avoid the following:

- Excess of dietary protein or protein malnutrition inducing catabolic state
- Prolonged fasting
- Catabolism during illness (intercurrent infection; brief febrile illness post vaccination)

## Evaluation of Relatives at Risk

IVA biochemical or molecular genetic testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of classic IVA.

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

Classic isovaleric acidemia (IVA) is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are presumed to be heterozygous for an *IVD* pathogenic variant.
- Once a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *IVD* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for an *IVD* 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.
- The neurologic phenotype of classic IVA and the frequency of acute metabolic crisis can vary widely among untreated individuals and family members with the same biallelic *IVD* pathogenic variants. This discrepancy is mostly explained by differences in the time of diagnosis as well as the start of and adherence to treatment.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** Unless an affected individual's reproductive partner also has classic IVA or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *IVD*.

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

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *IVD* 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 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, pathogenic mechanisms, 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 pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once the *IVD* pathogenic variants have been identified in an affected family member, prenatal 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.*

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)

United Kingdom
IVA

- **MedlinePlus**
  Isovaleric acidemia
- **International Society for Neonatal Screening (ISNS)**
  www.isns-neoscreening.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **Organic Acidemia Association**
  **Phone:** 763-559-1797
  **Fax:** 866-539-4060 (toll-free)
  **Email:** kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml

# 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.** Classic Isovaleric Acidemia: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *IVD* | 15q15.1 | Isovaleryl-CoA dehydrogenase, mitochondrial | IVD @ LOVD | IVD | IVD |

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 Classic Isovaleric Acidemia (View All in OMIM)

| | |
|---|---|
| 243500 | ISOVALERIC ACIDEMIA; IVA |
| 607036 | ISOVALERYL-CoA DEHYDROGENASE; IVD |

# Molecular Pathogenesis

Biallelic *IVD* pathogenic variants result in reduced enzyme activity in the mitochondrial isovaleryl-conenzyme A dehydrogenase and, subsequently, in accumulation of isovaleryl-conenzyme A and its metabolites.

**Mechanism of disease causation.** Loss of function

# Chapter Notes

## Author Notes

**Ulrike Mütze** is consultant for Pediatric Metabolic Medicine (Clinical Care, Metabolic and Newborn Screening [NBS] Laboratory) in the Division of Child Neurology and Metabolic Medicine at Heidelberg University Hospital, Germany. Her major research topic is the systematic evaluation of long-term outcome and lifelong care of individuals with inherited metabolic diseases identified by NBS, with a special focus on individuals with isovaleric acidemia (IVA). Her research goal is to set up long-term observation as a standard in NBS programs as a tool to iteratively evaluate and improve NBS programs and case definitions, allow guideline development, and inform long-term stratified treatment and care for established and future NBS conditions.

**Anna Reischl-Hajiabadi** is a pediatric resident with a special interest in pediatric metabolic medicine, NBS, and long-term observational studies.

**Stefan Kölker** is head of the Division of Child Neurology and Metabolic Medicine at Heidelberg University Hospital, Heidelberg, Germany. His major clinical and scientific interest is on inherited metabolic diseases and NBS programs. He is vice-coordinator of the European Reference Network for Hereditary Metabolic Disorders (MetabERN). With his team he has designed and established a set of interoperable patient registries (U-IMD, E-IMD, E-HOD) that are used for long-term observational studies on individuals with inherited metabolic diseases aiming to improve the knowledge base on these rare diseases, to improve diagnostic and therapeutic strategies, and to inform guideline development.

Long-term observational registries for individuals with inherited metabolic diseases that also includes individuals with IVA:

- European registry and network for Intoxication type Metabolic Diseases (E-IMD)
- Unified Registry for Inherited Metabolic Disorders (U-IMD)

Long-term outcome of individuals with inherited metabolic diseases after diagnosis by expanded newborn screening (NGS2020/NGS2025) – German Clinical Trials registration DRKS00013329

Drs Ulrike Mütze and Stefan Kölker are actively involved in clinical research regarding individuals with IVA. They would be happy to communicate with persons who have any questions regarding diagnosis of IVA or other considerations.

## Revision History

- 14 March 2024 (sw) Review posted live
- 26 June 2023 (sk) Original submission

# References

## Literature Cited

AWMF. Konfirmationsdiagnostik bei Verdacht auf angeborene Stoffwechselkrankheiten aus dem Neugeborenenscreening. Registernummber 027-021. December 31, 2019. Available online. Accessed 6-15-2020.

Boy N, Mühlhausen C, Maier EM, Ballhausen D, Baumgartner MR, Beblo S, Burgard P, Chapman KA, Dobbelaere D, Heringer-Seifert J, Fleissner S, Grohmann-Held K, Hahn G, Harting I, Hoffmann GF, Jochum F, Karall D, Konstantopoulous V, Krawinkel MB, Lindner M, Märtner EMC, Nuoffer JM, Okun JG, Plecko B, Posset R, Sahm K, Scholl-Bürgi S, Thimm E, Walter M, Williams M, Vom Dahl S, Ziagaki A, Zschocke J,

Kölker S. Recommendations for diagnosing and managing individuals with glutaric aciduria type 1: third revision. J Inherit Metab Dis. 2023;46:482-519. PubMed PMID: 36221165.

Couce ML, Aldamiz-Echevarría L, Bueno MA, Barros P, Belanger-Quintana A, Blasco J, García-Silva MT, Márquez-Armenteros AM, Vitoria I, Vives I, Navarrete R, Fernández-Marmiesse A, Pérez B, Pérez-Cerdá C. Genotype and phenotype characterization in a Spanish cohort with isovaleric acidemia. J Hum Genet. 2017;62:355-60. PubMed PMID: 27904153.

Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. "Classical" organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006;29:383-9. PubMed PMID: 16763906.

Ensenauer R, Vockley J, Willard JM, Huey JC, Sass JO, Edland SD, Burton BK, Berry SA, Santer R, Grunert S, Koch HG, Marquardt I, Rinaldo P, Hahn S, Matern D. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. Am J Hum Genet. 2004;75:1136-42. PubMed PMID: 15486829.

Forny P, Hörster F, Ballhausen D, Chakrapani A, Chapman KA, Dionisi-Vici C, Dixon M, Grünert SC, Grunewald S, Haliloglu G, Hochuli M, Honzik T, Karall D, Martinelli D, Molema F, Sass JO, Scholl-Bürgi S, Tal G, Williams M, Huemer M, Baumgartner MR. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: first revision. J Inherit Metab Dis. 2021;44:566-92. PubMed PMID: 33595124.

Grünert SC, Wendel U, Lindner M, Leichsenring M, Schwab KO, Vockley J, Lehnert W, Ensenauer R. Clinical and neurocognitive outcome in symptomatic isovaleric acidemia. Orphanet J Rare Dis. 2012;7:9. PubMed PMID: 22277694.

Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, Mandel H, Martinelli D, Pintos-Morell G, Santer R, Skouma A, Servais A, Tal G, Rubio V, Huemer M, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. J Inherit Metab Dis. 2019;42:1192-230. PubMed PMID: 30982989.

Hall PL, Marquardt G, McHugh DM, Currier RJ, Tang H, Stoway SD, Rinaldo P. Postanalytical tools improve performance of newborn screening by tandem mass spectrometry. Genet Med. 2014;16:889-95. PubMed PMID: 24875301.

Heringer J, Valayannopoulos V, Lund AM, Wijburg FA, Freisinger P, Barić I, Baumgartner MR, Burgard P, Burlina AB, Chapman KA, EC IS, Karall D, Mühlhausen C, Riches V, Schiff M, Sykut-Cegielska J, Walter JH, Zeman J, Chabrol B, Kölker S. Impact of age at onset and newborn screening on outcome in organic acidurias. J Inherit Metab Dis. 2016;39:341-53. PubMed PMID: 26689403.

Hertecant JL, Ben-Rebeh I, Marah MA, Abbas T, Ayadi L, Ben Salem S, Al-Jasmi FA, Al-Gazali L, Al-Yahyaee SA, Ali BR. Clinical and molecular analysis of isovaleric acidemia patients in the United Arab Emirates reveals remarkable phenotypes and four novel mutations in the IVD gene. Eur J Med Genet. 2012;55:671-6. PubMed PMID: 22960500.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kölker S, Garcia-Cazorla A, Valayannopoulos V, Lund AM, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, Zeman J, Dionisi-Vici C, Barić I, Karall D, Augoustides-Savvopoulou P, Aksglaede L, Arnoux JB, Avram P, Baumgartner MR, Blasco-Alonso J, Chabrol B, Chakrapani A, Chapman K, EC IS, Couce ML, de Meirleir

L, Dobbelaere D, Dvorakova V, Furlan F, Gleich F, Gradowska W, Grünewald S, Jalan A, Häberle J, Haege G, Lachmann R, Laemmle A, Langereis E, de Lonlay P, Martinelli D, Matsumoto S, Mühlhausen C, de Baulny HO, Ortez C, Peña-Quintana L, Ramadža DP, Rodrigues E, Scholl-Bürgi S, Sokal E, Staufner C, Summar ML, Thompson N, Vara R, Pinera IV, Walter JH, Williams M, Burgard P. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation. J Inherit Metab Dis. 2015a;38:1041-57. PubMed PMID: 25875215.

Kölker S, Valayannopoulos V, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, Zeman J, Dionisi-Vici C, Barić I, Karall D, Arnoux JB, Avram P, Baumgartner MR, Blasco-Alonso J, Boy SP, Rasmussen MB, Burgard P, Chabrol B, Chakrapani A, Chapman K, Cortès ISE, Couce ML, de Meirleir L, Dobbelaere D, Furlan F, Gleich F, González MJ, Gradowska W, Grünewald S, Honzik T, Hörster F, Ioannou H, Jalan A, Häberle J, Haege G, Langereis E, de Lonlay P, Martinelli D, Matsumoto S, Mühlhausen C, Murphy E, de Baulny HO, Ortez C, Pedrón CC, Pintos-Morell G, Pena-Quintana L, Ramadža DP, Rodrigues E, Scholl-Bürgi S, Sokal E, Summar ML, Thompson N, Vara R, Pinera IV, Walter JH, Williams M, Lund AM, Garcia-Cazorla A. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis. 2015b;38:1059-74. PubMed PMID: 25875216.

Moorthie S, Cameron L, Sagoo GS, Bonham JR, Burton H. Systematic review and meta-analysis to estimate the birth prevalence of five inherited metabolic diseases. J Inherit Metab Dis. 2014;37:889-98. PubMed PMID: 25022222.

Murko S, Aseman AD, Reinhardt F, Gramer G, Okun JG, Mütze U, Santer RJJR. Neonatal screening for isovaleric aciduria: Reducing the increasingly high false-positive rate in Germany. JIMD Rep. 2022;64:114-20. PubMed PMID: 36636590.

Mütze U, Garbade SF, Gleich F, Lindner M, Freisinger P, Hennermann JB, Thimm E, Gramer G, Posset R, Krämer J, Grünert SC, Hoffmann GF, Kölker S. Long-term anthropometric development of individuals with inherited metabolic diseases identified by newborn screening. J Inherit Metab Dis. 2023a;46:15-27. PubMed PMID: 36134599.

Mütze U, Henze L, Gleich F, Lindner M, Grünert SC, Spiekerkoetter U, Santer R, Blessing H, Thimm E, Ensenauer R, Weigel J, Beblo S, Arélin M, Hennermann JB, Marquardt T, Marquardt I, Freisinger P, Krämer J, Dieckmann A, Weinhold N, Keller M, Walter M, Schiergens KA, Maier EM, Hoffmann GF, Garbade SF, Kölker S. Newborn screening and disease variants predict neurological outcome in isovaleric aciduria. J Inherit Metab Dis. 2021;44:857-70. PubMed PMID: 33496032.

Mütze U, Henze L, Schröter J, Gleich F, Lindner M, Grünert SC, Spiekerkoetter U, Santer R, Thimm E, Ensenauer R, Weigel J, Beblo S, Arélin M, Hennermann JB, Marquardt I, Freisinger P, Krämer J, Dieckmann A, Weinhold N, Schiergens KA, Maier EM, Hoffmann GF, Garbade SF, Kölker S. Isovaleric aciduria identified by newborn screening: strategies to predict disease severity and stratify treatment. J Inherit Metab Dis. 2023b;46:1063-77. PubMed PMID: 37429829.

Pinto A, Daly A, Evans S, Almeida MF, Assoun M, Belanger-Quintana A, Bernabei S, Bollhalder S, Cassiman D, Champion H, Chan H, Dalmau J, de Boer F, de Laet C, de Meyer A, Desloovere A, Dianin A, Dixon M, Dokoupil K, Dubois S, Eyskens F, Faria A, Fasan I, Favre E, Feillet F, Fekete A, Gallo G, Gingell C, Gribben J, Kaalund-Hansen K, Horst N, Jankowski C, Janssen-Regelink R, Jones I, Jouault C, Kahrs GE, Kok IL, Kowalik A, Laguerre C, Le Verge S, Lilje R, Maddalon C, Mayr D, Meyer U, Micciche A, Robert M, Rocha JC, Rogozinski H, Rohde C, Ross K, Saruggia I, Schlune A, Singleton K, Sjoqvist E, Stolen LH, Terry A, Timmer C, Tomlinson L, Tooke A, Vande Kerckhove K, van Dam E, van den Hurk T, van der Ploeg L, van Driessche M, van Rijn M, van Teeffelen-Heithoff A, van Wegberg A, Vasconcelos C, Vestergaard H, Vitoria I, Webster D, White FJ, White L, Zweers H, MacDonald A. Dietary practices in isovaleric acidemia: a European survey. Molecular genetics and metabolism reports. 2017;12:16-22. PubMed PMID: 28275552.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint

consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schiff M, Benoist JF, Brassier A, Vockley J. Disorders of branched-chain amino acid metabolism. In: Blau N, Dionisi Vici C, Ferreira CR, Vianey-Saban C, van Karnebeek CDM, eds. *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*, vol 2. Berlin: Springer; 2022:391-400.

Schlune A, Riederer A, Mayatepek E, Ensenauer R. Aspects of newborn screening in isovaleric acidemia. Int J Neonatal Screen. 2018;4:7. PubMed PMID: 33072933.

Sezer T, Balci O. Infantile spasms during acute metabolic decompensation in an infant with isovaleric acidemia. J Clin Neurol. 2016;12:376-7. PubMed PMID: 27165427.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Tanaka K. Isovaleric acidemia: personal history, clinical survey and study of the molecular basis. Prog Clin Biol Res. 1990;321:273-90. PubMed PMID: 2326294.

Tavares de Almeida I, Ribes A. Organic acids. In: Blau N, Dionisi Vici C, Ferreira CR, Vianey-Saban C, van Karnebeek CDM, eds. *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*, 2nd ed. Cham: Springer Nature Switzerland AG; 2022:51-64.

Tuncel AT, Boy N, Morath MA, Hörster F, Mütze U, Kölker S. Organic acidurias in adults: late complications and management. J Inherit Metab Dis. 2018;41:765-76. PubMed PMID: 29335813.

Vockley J, Ensenauer R. Isovaleric acidemia: new aspects of genetic and phenotypic heterogeneity. Am J Med Genet C Semin Med Genet. 2006;142C:95-103. PubMed PMID: 16602101.

Zaunseder E, Mütze U, Garbade SF, Haupt S, Feyh P, Hoffmann GF, Heuveline V, Kölker S. Machine learning methods improve specificity in newborn screening for isovaleric aciduria. Metabolites. 2023;13:304. PubMed PMID: 36837923.

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