# DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| **DISORDERS OF PHENYLALANINE AND TYROSINE METABOLISM** | | | |
| Phenylketonuria (PKU), with classic and mild forms (261600) | Phenylalanine hydroxylase | PAH (12q24.1)* | **Biochemical profile:** Elevated plasma phenylalanine<br>**Clinical features:** Intellectual disability, behavioral problems<br>**Treatment:** Dietary phenylalanine restriction, tyrosine supplementation |
| Dihydropteridine reductase deficiency (261630) | Dihydropteridine reductase | QDPR (4p15.31)* | **Biochemical profile:** Elevated plasma phenylalanine, high urine biopterin, low plasma biopterin<br>**Clinical features:** Similar to mild PKU, but if neurotransmitter deficiency is unrecognized, development of intellectual disability, seizures, and dystonia<br>**Treatment:** Dietary phenylalanine restriction, tyrosine supplementation, folinic acid, neurotransmitter replacement |
| Pterin-4α-carbinolamine dehydratase deficiency (264070) | Pterin-4α-carbinolamine dehydratase | PCBD (10q22)* | **Biochemical profile:** Elevated plasma phenylalanine, high urine neopterin and primapterin, low plasma biopterin<br>**Clinical features:** Similar to mild PKU, but if neurotransmitter deficiency is unrecognized, development of intellectual disability, seizures, and dystonia<br>**Treatment:** Dietary phenylalanine restriction, tyrosine supplementation, neurotransmitter replacement |
| Biopterin synthesis deficiency | GTP-cyclohydrolase (233910) | GCH1 (14q22)* | **Biochemical profile:** Elevated plasma phenylalanine, low urine biopterin, low (GCH) or high (PTS and SPR) urine neopterin<br>**Clinical features:** Similar to mild PKU, but if neurotransmitter deficiency is unrecognized, development of intellectual disability, seizures, and dystonia<br>**Treatment:** Tetrahydrobiopterin and neurotransmitter supplementation |
| | 6-Pyruvoyl-tetrahydropterin synthase (261640) | PTS (11q22-q23)* | |
| | Sepiapterin reductase (182125) | SPR (2p14-p12)* | |
| Tyrosinemia type I (hepatorenal; 276700) | Fumarylacetoacetate hydrolase | FAH (15q23-q25)* | **Biochemical profile:** Elevated plasma tyrosine, elevated plasma and urinary succinylacetone<br>**Clinical features:** Cirrhosis, acute liver failure, peripheral neuropathy, Fanconi syndrome<br>**Treatment:** Dietary phenylalanine, tyrosine, and methionine restriction; 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC); liver transplantation |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Tyrosinemia type II (oculocutaneous; 276600) | Tyrosine aminotransferase | TAT (16q22.1-q22.3)* | **Biochemical profile:** Elevated plasma tyrosine and phenylalanine<br>**Clinical features:** Intellectual disability, palmoplantar hyperkeratitis, corneal ulcers<br>**Treatment:** Dietary phenylalanine and tyrosine restriction |
| Tyrosinemia type III (276710) | 4-Hydroxyphenylpyruvate dioxygenase | HPD (12q24-qter)* | **Biochemical profile:** Elevated plasma tyrosine, elevated urinary 4-hydroxyphenyl derivatives<br>**Clinical features:** Developmental delay, seizures, ataxia<br>**Treatment:** Dietary phenylalanine and tyrosine restriction, ascorbate supplementation |
| Transient tyrosinemia | 4-Hydroxyphenylpyruvate dioxygenase | Not genetic | **Biochemical profile:** Elevated plasma phenylalanine and tyrosine<br>**Clinical features:** Usually occurring in premature infants; mostly asymptomatic<br>Occasionally poor feeding and lethargy<br>**Treatment:** Tyrosine restriction and ascorbate supplementation for symptomatic patients only |
| Hawkinsinuria (140350) | 4-Hydroxyphenylpyruvate dioxygenase complex | HPD (12q24-qter)* | **Biochemical profile:** Mild hypertyrosinemia, elevated urinary hawkinsin<br>**Clinical features:** Failure to thrive, ketotic metabolic acidosis<br>**Treatment:** Dietary phenylalanine and tyrosine restriction, ascorbate supplementation |
| Alkaptonuria (203500) | Homogentisate oxidase | HGD (3q21-q23)* | **Biochemical profile:** Elevated urine homogentisic acid<br>**Clinical features:** Dark urine, ochronosis, arthritis<br>**Treatment:** None; ascorbate supplementation to reduce pigmentation |
| Oculocutaneous albinism type I (A and B; 203100) | Tyrosinase | TYR (11q21)* | **Biochemical profile:** No abnormality in plasma and urine amino acids, absent (IA) or decreased (IB) tyrosinase<br>**Clinical features:** Absent (IA) or decreased (IB) pigment in skin, hair, iris, and retina; nystagmus; blindness; skin cancer<br>**Treatment:** Protection of skin and eyes from actinic radiation |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| **DISORDERS OF BRANCHED-CHAIN AMINO ACID (VALINE, LEUCINE, ISOLEUCINE) METABOLISM** | | | |
| Maple syrup urine disease, or branched-chain ketoaciduria (248600) | Branched-chain α-keto-acid dehydrogenase complex (BCKD) | | **Biochemical profile:** Elevated plasma valine, leucine, isoleucine, and alloisoleucine<br>Clinical features (molecular forms do not correlate with clinical forms except that a high percentage of type II mutations are associated with thiamin responsiveness): |
| Type IA | BCKD E1α component | BCKDHA (19q13)* | In classic form, hypertonia, seizures, coma, death |
| Type IB | BCKD E1β component | BCKDHB (6p22-p21)* | In intermediate form, intellectual disability, neurologic symptoms, full-blown picture developing with stress |
| Type II | BCKD E2 component | DBT (1p31)* | In intermittent form, symptoms only with stress (eg, fever, infection) |
| Type III | BCKD E3 component | DLD (7q31-q32)* | In thiamin-responsive form, features similar to mild intermediate form<br>In E3 subunit deficient form, features similar to intermediate form but accompanied by severe lactic acidosis because E3 is needed for pyruvate dehydrogenase and a-ketoglutarate dehydrogenase<br>**Acute Treatment:** Peritoneal dialysis, hemodialysis, or both; aggressive nutrition management, including high-dose glucose, insulin, and special hyperalimentation<br>**Chronic Treatment:** Dietary branched-chain amino acid restriction, thiamin supplementation as needed |
| Propionic acidemia (606054) | Propionyl-CoA carboxylase | | **Biochemical profile:** Elevated plasma glycine, urine methylcitrate, 3-hydroxypropionate, propionylglycine, and tiglylglycine |
| Type I | α-Subunit | PCCA (13q32)* | **Clinical features:** Hypotonia, vomiting, lethargy, coma, ketoacidosis, hypoglycemia, hyperammonemia, bone marrow suppression, growth delay, intellectual disability, physical disability |
| Type II | β-Subunit | PCCB (3q21-q22)* | **Treatment:** During acute episodes, high-dose glucose and aggressive fluid resuscitation<br>For extreme hyperammonemia, may need hemodialysis or peritoneal dialysis<br>For long-term management, controlled intake of threonine, valine, isoleucine, and methionine; carnitine supplementation; biotin for responsive patients (see also Multiple carboxylase deficiency and Biotinidase deficiency, below) |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Multiple carboxylase deficiency (253270) | Holocarboxylase synthetase | HLCS (21q22.1)* | **Biochemical profile:** Same as for propionic acidemia but also elevated lactate and 3-methylcrotonate<br>**Clinical features:** Skin rash, alopecia, seizures, hypotonia, developmental delay, ketoacidosis, defective T- and B-cell immunity, hearing loss<br>**Treatment:** Biotin 5–10 mg/day |
| Biotinidase deficiency (253260) | Biotinidase | BTD (3p25)* | Similar to multiple carboxylase deficiency |
| Methylmalonic acidemia (mut defects; 251000) | Methylmalonyl-CoA mutase<br>$Mut^0$ (no enzyme activity)<br>$Mut^-$ (some residual enzyme activity) | MUT (6p21)* | **Biochemical profile:** Elevated plasma glycine; increased urine methylmalonate, 3-hydroxypropionate, methylcitrate, and tiglylglycine<br>**Clinical features:** Hypotonia, vomiting, lethargy, coma, ketoacidosis, hypoglycemia, hyperammonemia, bone marrow suppression, growth delay, intellectual disability, and physical disability<br>**Treatment:** During acute episodes, high-dose glucose and aggressive fluid resuscitation<br>For extreme hyperammonemia, may need hemodialysis or peritoneal dialysis<br>For long-term management, controlled intake of threonine, valine, isoleucine, and methionine; carnitine supplementation; vitamin $B_{12}$ for patients with mut- type |
| Methylmalonic acidemia (cblA; 251100) | Mitochondrial cobalamin translocase | MMAA (4q31.1-q31.2)* | **Biochemical profile:** Similar to methylmalonic acidemia due to mutase deficiency<br>**Clinical features:** Similar to methylmalonic acidemia due to mutase deficiency<br>**Treatment:** Responsive to high-dose hydroxycobalamin |
| Methylmalonic acidemia (cblB; 251110) | ATP:cob(1)alamin adenosyl transferase | MMMB (12q24)* | **Biochemical profile:** Similar to methylmalonic acidemia due to mutase deficiency<br>**Clinical features:** Similar to methylmalonic acidemia due to mutase deficiency<br>**Treatment:** Responsive to high-dose hydroxycobalamin |

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|---|---|---|---|
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (cblC; 277400) | Methylmalonyl-CoA mutase and methylene tetrahydrofolate: homocysteine methyltransferase | Genetically heterogeneous | **Biochemical profile:** Similar to methylmalonic acidemia cblA and cblB but also homocystinemia, homocystinuria, low methionine, and high cystathionine; normal serum cobalamin<br>**Clinical features:** Similar to cblA and cblB but also megaloblastic anemia<br>**Treatment:** Protein restriction, high-dose hydroxycobalamin |
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (cblD; 277410) | Not determined | Genetically heterogeneous | Similar to methylmalonic acidemia cblC |
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (cblF; 277380) | Defective lysosomal release of cobalamin | Genetically heterogeneous | Similar to methylmalonic acidemia cblC |
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (intrinsic factor deficiency; 261000) | Intrinsic factor | GIF (11q13)* | Similar to methylmalonic acidemia cblC |
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (Imerslund-Graesbeck syndrome; 261100) | Cubilin (intrinsic factor receptor) | CUBN (10p12.1)* | Similar to methylmalonic acidemia cblC |
| Methylmalonic acidemia-homocystinuria-megaloblastic anemia (transcobalamin II deficiency; 275350) | Transcobalamin II | TC2 (22q11.2)* | Similar to methylmalonic acidemia cblC |
| Methylmalonic semialdehyde dehydrogenase deficiency with mild methylmalonic acidemia (603178) | Methylmalonic semialdehyde dehydrogenase (see also disorders of β- and γ-amino acids, below) | ALDH6A1 (14q24.1) | **Biochemical profile:** Moderate urine methylmalonate<br>**Clinical features:** Developmental delay, seizures<br>**Treatment:** No effective treatment |
| Methylmalonic acidemia-homocystinuria (cblH; 606169) | Not determined | Genetically heterogeneous | Similar to methylmalonic acidemia cblA |

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| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Isovaleric acidemia (243500) | Isovaleryl-CoA dehydrogenase | IVD (15q14-q15)* | **Biochemical profile:** Isovaleryl glycine, 3-hydroxyisovalerate<br>**Clinical features:** Characteristic sweaty feet odor, vomiting, lethargy, acidosis, intellectual disability, bone marrow suppression, hypoglycemia; ketoacidosis, hyperammonemia, neonatal death<br>**Treatment:** Controlled leucine intake, glycine, carnitine |
| 3-Methylcrotonyl-CoA carboxylase deficiency | 3-Methylcrotonyl CoA carboxylase | | **Biochemical profile:** Elevated 3-hydroxyisovalerate, 3-methylcrontylglycine, and 3-hydroxyisovalerylcarnitine |
| Type I (210200) | α-Subunit | MCCC1 (3q25-q27)* | **Clinical features:** Episodic vomiting, acidosis, hypoglycemia, hypotonia, intellectual disability, coma; sometimes asymptomatic intellectual disability |
| Type II (210210) | β-Subunit | MCCC2 (5q12-q13)* | **Treatment:** Controlled leucine intake (see also Multiple carboxylase deficiency and Biotinidase deficiency, above) |
| 3-Methylglutaconic aciduria type I (250950) | 3-Methylglutaconyl-CoA hydratase | AUH (9)* | **Biochemical profile:** Elevated urine 3-methylglutaconate and 3-hydroxyisolvalerate<br>**Clinical features:** Acidosis, hypotonia, hepatomegaly, speech delay<br>**Treatment:** Carnitine; benefit of leucine restriction unclear |
| 3-Methylglutaconic aciduria type II (Barth syndrome; 302060) | Tafazzin | TAZ (Xq28)* | **Biochemical profile:** Elevated urine 3-methylglutaconate and 3-methylglutarate<br>**Clinical features:** Myopathy, dilated cardiomyopathy, mitochondrial abnormality, neutropenia, developmental delay<br>**Treatment:** Pantothenic acid |
| 3-Methylglutaconic aciduria type III (Costeff optic atrophy; 258501) | Not determined | OPA3 (19q13)* | **Biochemical profile:** Elevated urine 3-methylglutaconate and 3-methylglutarate<br>**Clinical features:** Optic atrophy, ataxia, spasticity, choreiform movement<br>**Treatment:** No effective treatment |
| 3-Methylglutaconic aciduria type IV (250951) | Not determined | Not determined | **Biochemical profile:** Elevated urine 3-methylglutaconate and 3-methylglutarate<br>**Clinical features:** Variable expression, growth and developmental delay, hypotonia, seizures, optic atrophy, deafness, cardiomyopathy, acidosis<br>**Treatment:** No effective treatment |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (246450) | 3-Hydroxy-3-methylglutaryl-CoA lyase | HMGCL (1pter-p33)* | **Biochemical profile:** Elevated urine 3-hydroxy-3-methylglutarate, 3-methylglutaconate, and 3-hydroxyisovalerate; elevated plasma 3-methylglutarylcarnitine<br>**Clinical features:** Reye-like syndrome, vomiting, hypotonia, acidosis, hypoglycemia, lethargy, hyperammonemia without ketosis<br>**Treatment:** Restricted leucine intake, control of hypoglycemia |
| Mevalonic aciduria (251170, 260920) | Mevalonate kinase | MVK (12q24)* | **Biochemical profile:** Elevated creatine kinase, transaminase, leukotriene, and urinary mevalonic acid; decreased cholesterol<br>**Clinical features:**<br>In classic form, short stature, hypotonia, developmental delay, dysmorphic features, cataracts, vomiting, diarrhea, hepatosplenomegaly, arthralgia, lymphadenopathy, cerebral and cerebellar atrophy, anemia, thrombocytopenia, early death<br>In hyper IgD form, recurrent febrile episodes, vomiting, diarrhea, arthralgia, abdominal pain, rash, splenomegaly, elevated serum IgD and IgA levels<br>**Treatment:** No effective treatment; corticosteroids during acute attacks possibly helpful |
| Mitochondrial acetoacetyl-CoA thiolase deficiency (607809) | Acetyl-CoA thiolase | ACAT1 (11q22.3-a23.1)* | **Biochemical profile:** Elevated urine 2-methyl-3-hydroxybutyrate and 2-methylacetoacetate, elevated plasma tiglylglycine<br>**Clinical features:** Episodes of ketoacidosis, vomiting, diarrhea, coma, intellectual disability<br>**Treatment:** Low-protein diet, controlled isoleucine intake |
| Isobutyryl-CoA dehydrogenase deficiency | Isobutyryl-CoA dehydrogenase | Not determined | **Biochemical profile:** Elevated C-4 carnitine, low free carnitine<br>**Clinical features:** Anemia, cardiomyopathy<br>**Treatment:** Carnitine |
| 3-Hydroxyisobutyryl-CoA deacylase deficiency (methacrylic aciduria; 250620) | 3-Hydroxyisobutyryl-CoA deacylase | Not determined | **Biochemical profile:** Elevated *S*-(2-carboxypropyl)-cysteine and *S*-(2-carboxypropyl)-cysteamine<br>**Clinical features:** Growth and developmental delay, dysmorphic feature, vertebral anomaly, CNS malformations, death<br>**Treatment:** No effective treatment |

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|---|---|---|---|
| 3-Hydroxyisobutyric aciduria (236795) | 3-Hydroxyisobutyrate dehydrogenase | HIBADH (chromosomal location not determined) | **Biochemical profile:** Elevated urine 3-hydroxyisobutyrate; in 50% patients, elevated lactate<br>**Clinical features:** Dysmorphic features, CNS malformations, hypotonia, ketoacidosis<br>**Treatment:** Low-protein diet, carnitine |
| 2-Methylbutyryl glycinuria (600301) | Short branched-chain acyl-CoA dehydrogenase | ACADSB (10q25-q26)* | **Biochemical profile:** Elevated urine 2-methylbutyrulglycine<br>**Clinical features:** Hypotonia, muscular atrophy, lethargy, hypoglycemia, hypothermia<br>**Treatment:** No effective treatment |
| Ethylmalonic encephalopathy (602473) | Mitochondrial protein of undetermined function | ETHE1 (19q13.32)* | **Biochemical profile:** Elevated urine ethylmalonic and methylsuccinic acids, elevated serum lactate<br>**Clinical features:** Retinopathy, acrocyanosis, diarrhea, petechiae, developmental delay, intellectual disability, extrapyramidal symptoms, ataxia, seizures, hyperintense lesions in the basal ganglia<br>**Treatment:** No effective treatment |
| Malonic aciduria (248360) | Malonyl-CoA decarboxylase | MLYCD (16q24)* | **Biochemical profile:** Elevated lactate, malonate, methylmalonate, and malonylcarnitine<br>**Clinical features:** Hypotonia, developmental delay, hypoglycemia, acidosis<br>**Treatment:** No effective treatment; low-fat, high-carbohydrate diet<br>Carnitine possibly helpful in some patients |
| Hypervalinemia or hyperisoleucine-hyperleucinemia (277100) | Mitochondrial branched-chain aminotransferase 2 | BCAT2 (19q13) | **Biochemical profile:** Elevated urine and serum valine<br>**Clinical features:** Growth retardation<br>**Treatment:** Controlled valine intake |
| **DISORDERS OF METHIONINE AND SULFUR METABOLISM** | | | |
| Homocystinuria (236200) | Cystathionine β-synthase | CBS (21q22.3)* | **Biochemical profile:** Methioninuria, homocystinuria<br>**Clinical features:** Osteoporosis, scoliosis, fair complexion, ectopia lentis, progressive intellectual disability, thromboembolism<br>**Treatment:** Pyridoxine, folate, betaine for unresponsive patients, low methionine diet with some L-cysteine supplementation |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

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|---|---|---|---|
| Methylenetetrahydrofolate reductase deficiency (236250) | Methylenetetrahydrofolate reductase | MTHFR (1p36.3)* | **Biochemical profile:** Low to normal plasma methionine, homocystinemia, homocystinuria<br>**Clinical features:** Varies from asymptomatic to microcephaly, hypotonia, seizures, gait abnormality, and intellectual disability to apnea, coma, and death<br>**Treatment:** Pyridoxine, folate (folic acid), hydroxycobalamin, methionine, betaine |
| Methylmalonic acidemia-homocystinuria (cblE; 236270) | Methionine synthase reductase | MTRR (5p15)* | **Biochemical profile:** Homocystinuria, homocystinemia, low plasma methionine, no methylmalonic aciduria, normal B12 and folate<br>**Clinical features:** Feeding difficulty, growth failure, intellectual disability, ataxia, cerebral atrophy<br>**Treatment:** Hydroxycobalamin, folate, L-methionine |
| Methylmalonic acidemia-homocystinuria (cblG; 250940) | Methylene tetrahydrofolate homocysteine methyltransferase | MTR (1q43)* | Same as methylmalonic acidemia-homocystinuria cblE |
| Hypermethioninemia (250850) | Methionine adenosyltransferase I and III | MAT1A (10q22)* | **Biochemical profile:** Elevated plasma methionine<br>**Clinical features:** Mainly asymptomatic, fetid breath<br>**Treatment:** None needed |
| Cystathioninuria (219500) | γ-Cystathionase | CTH (16)* | **Biochemical profile:** Cystathioninuria<br>**Clinical features:** Usually normal; intellectual disability reported<br>**Treatment:** Pyridoxine |
| Sulfite oxidase deficiency (606887) | Sulfite oxidase | SUOX (12q13)* | **Biochemical profile:** Elevated urine sulfite, thiosulfate, and *S*-sulfocysteine; decreased sulfate<br>**Clinical features:** Developmental delay, ectopia lentis, eczema, delayed dentition, fine hair, hemiplegia, infantile hypotonia, hypertonia, seizures, choreoathetosis, ataxia, dystonia, death<br>**Treatment:** No effective treatment |

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|---|---|---|---|
| Molybdenum cofactor defect (252150) | MOCS1A and MOCS1B proteins | MCOS1 (14q24)* | **Biochemical profile:** Elevated urinary sulfite, thiosulfate, *S*-sulfocysteine, taurine, hypoxanthine, and xanthine; decreased sulfate and urate<br>**Clinical features:** Similar to sulfite oxidase deficiency but also urinary stones<br>**Treatment:** No effective treatment<br>Low sulfur diet possibly helpful in patients with milder symptoms |
| | Molybdopterin synthase | MCOS2 (6p21.3)* | |
| | Gephyrin | GEPH (5q21)* | |
| **UREA CYCLE AND RELATED DISORDERS** | | | |
| Ornithine-transcarbamoylase (OTC) deficiency (311250) | OTC | OTC (Xp21.1)* | **Biochemical profile:** Elevated ornithine and glutamine, decreased citrulline and arginine, markedly increased urine orotate<br>**Clinical features:** In males, recurrent vomiting, irritability, lethargy, hyperammonemic coma, cerebral edema, spasticity, intellectual disability, seizures, death<br>In female carriers, variable manifestations, ranging from growth delay, small stature, protein aversion, and postpartum hyperammonemia to symptoms as severe as those in males with the deficiency<br>**Treatment:** Hemodialysis for emergent hyperammonemic crisis, Na benzoate, Na phenylacetate, Na phenylbutyrate, low-protein diet supplemented with essential amino acid mixture and arginine, citrulline, experimental attempts at gene therapy, liver transplantation (which is curative) |
| *N*-Acetylglutamate synthetase deficiency (237310) | *N*-Acetylglutamate synthetase | NAGS (17q21.31) | **Biochemical profile:** Similar to OTC deficiency except for normal to low urine orotate<br>**Clinical features:** Similar to OTC deficiency except carriers are asymptomatic<br>**Treatment:** Similar to OTC deficiency but also N-carbamylglutamate supplementation |
| Carbamoyl phosphate synthetase (CPS) deficiency (237300) | Carbamoyl phosphate synthetase | CPS1 (2q35)* | **Biochemical profile:** Similar to OTC deficiency except for normal to low urine orotate<br>**Clinical features:** Similar to OTC deficiency except carriers are asymptomatic<br>**Treatment:** Na benzoate and arginine |

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|---|---|---|---|
| Citrullinemia type I (215700) | Argininosuccinic acid synthetase | ASS (9q34)* | **Biochemical profile:** High plasma citrulline and glutamine, citrullinuria, orotic aciduria<br>**Clinical features:** Episodic hyperammonemia, growth failure, protein aversion, lethargy, vomiting, coma, seizures, cerebral edema, developmental delay<br>**Treatment:** Similar to that for OTC deficiency except citrulline supplementation is not recommended |
| Citrullinemia type II (603814, 603471) | Citrin | SCL25A13 (7q21.3)* | **Biochemical profile:** Elevated plasma citrulline, methionine, galactose, and bilirubin<br>**Clinical features:** With neonatal onset, cholestasis resolved by 3 mo<br>With adult onset, enuresis, delayed menarche, sleep reversal, vomiting, delusions, hallucinations, psychosis, coma<br>**Treatment:** No clear treatment |
| Argininosuccinic aciduria (207900) | Argininosuccinate lyase | ASL (7cen-q11.2)* | **Biochemical profile:** Elevated plasma citrulline and glutamine, elevated urine argininosuccinate<br>**Clinical features:** Episodic hyperammonemia, hepatic fibrosis, elevated liver enzymes, hepatomegaly, protein aversion, vomiting, seizures, intellectual disability, ataxia, lethargy, coma, trichorrhexis nodosa<br>**Treatment:** Arginine supplementation |
| Argininemia (107830) | Arginase I | ARG1 (6q23)* | **Biochemical profile:** Elevated plasma arginine, diaminoaciduria (argininuria, lysinuria, cystinuria, ornithinuria), orotic aciduria, pyrimidinuria<br>**Clinical features:** Growth and developmental delay, anorexia, vomiting, seizures, spasticity, irritability, hyperactivity, protein intolerance, hyperammonemia<br>**Treatment:** Low-protein diet, benzoate, phenylacetate |
| Lysinuric protein intolerance (dibasic aminoaciduria II; 222700) | Dibasic amino acid transporter | SLC7A7 (14q11.2)* | **Biochemical profile:** Elevated urine lysine, ornithine, and arginine<br>**Clinical features:** Protein intolerance, episodic hyperammonemia, growth and developmental delay, diarrhea, vomiting, hepatomegaly, cirrhosis, leucopenia, osteopenia, skeletal fragility, coma<br>**Treatment:** Low-protein diet, citrulline |

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|---|---|---|---|
| Hyperornithinemia, hyperammonemia, and homocitrullinemia (238970) | Mitochondrial ornithine translocase | SLC25A15 (13q14)* | **Biochemical profile:** Elevated plasma ornithine, homocitrullinemia<br>**Clinical features:** Intellectual disability, progressive spastic paraparesis, episodic confusion, hyperammonemia, dyspraxia, seizures, vomiting, retinopathy, abnormal nerve conduction and evoked potentials, leukodystrophy<br>**Treatment:** Lysine, ornithine, or citrulline supplementation |
| Ornithinemia (258870) | Ornithine aminotransferase | OAT (10q26)* | **Biochemical profile:** Elevated plasma ornithine and urine ornithine, lysine, and arginine; low plasma lysine, glutamic acid, and glutamine<br>**Clinical features:** Myopia, night blindness, blindness, progressive loss of peripheral vision, progressive gyrate atrophy of choroid and retina, mild proximal hypotonia, myopathy<br>**Treatment:** Pyridoxine, low-arginine diet, lysine and a-aminoisobutyrate to increase renal loss of ornithine; proline or creatine supplementation |
| Hyperinsulinism-hyperammonemia syndrome (606762) | Hyperactivity of glutamate dehydrogenase | GLUD1 (10q23.3)* | **Biochemical profile:** Elevated urine α-ketoglutarate<br>**Clinical features:** Seizures, recurrent hypoglycemia, hyperinsulinism, asymptomatic hyperammonemia<br>**Treatment:** Prevention of hypoglycemia |
| **DISORDERS OF PROLINE AND HYDROXYPROLINE METABOLISM** | | | |
| Hyperprolinemia, type I (239500) | Proline oxidase (proline dehydrogenase) | PRODH (22q11.2)* | **Biochemical profile:** Elevated plasma proline and urinary proline, hydroxyproline, and glycine<br>**Clinical features:** Usually benign; hereditary nephritis, nerve deafness<br>**Treatment:** None needed |
| Hyperprolinemia, type II (239510) | Δ1-Pyrroline-5-carboxylate dehydrogenase | P5CDH (1p36)* | **Biochemical profile:** Elevated plasma proline and pyrroline-5-carboxylate (P5C); elevated urinary P5C, Δ1-pyrroline-5-carboxylate, proline, hydroxyproline, and glycine<br>**Clinical features:** During childhood, seizures, intellectual disability<br>During adulthood, benign<br>**Treatment:** None needed |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Δ1-Pyrroline-5-carboxylate synthetase deficiency (138250) | Δ1-Pyrroline-5-carboxylate synthetase | PYCS (10q24.3)* | **Biochemical profile:** Low plasma proline, citrulline, arginine, and ornithine<br>**Clinical features:** Hyperammonemia, cataracts, intellectual disability, joint laxity<br>**Treatment:** Avoidance of fasting |
| Hyperhydroxyprolinemia (237000) | 4-Hydroxyproline oxidase | Not determined | **Biochemical profile:** Hydroxyprolinemia<br>**Clinical features:** Disease association not proven<br>**Treatment:** None needed |
| Prolidase deficiency (170100) | Prolidase | PEPD (19q12-q13.11)* | **Biochemical profile:** Amino acid profile normal in unhydrolyzed urine, but excessive proline and hydroxyproline in acid-hydrolyzed urine<br>**Clinical features:** Skin ulcers, frequent infections, dysmorphic features, immunodeficiency, intellectual disability<br>**Treatment:** Proline supplement, $Mn^{++}$ and ascorbic acid, essential amino acids, blood transfusion (packed RBC), topical proline and glycine ointment |
| **DISORDERS OF β- AND γ-AMINO ACIDS** | | | |
| Hyper-β-alaninemia (237400) | β-Alanine-α-ketoglutarate aminotransferase | Not determined | **Biochemical profile:** Elevated urinary β-alanine, taurine, γ-aminobutyrate (GABA), and β-aminoisobutyrate<br>**Clinical features:** Seizures, somnolence, death<br>**Treatment:** Pyridoxine |
| Methylmalonate/malonate semialdehyde dehydrogenase deficiency with 3-amino and 3-hydroxy aciduria (236795) | Methylmalonate/malonate semialdehyde dehydrogenase | ALDH6A1 (14q24.3)* | **Biochemical profile:** Elevated 3-hydroxyisobutyrate 3-aminoisobutyrate, 3-hydroxypropionate β-alanine, and 2-ethyl-3-hydroxypropionate<br>**Clinical features:** None to mild<br>**Treatment:** Not determined |
| Methylmalonic semialdehyde dehydrogenase deficiency with mild methylmalonic acidemia | Methylmalonic semialdehyde dehydrogenase (see also Branched-chain amino acid metabolism, above) | ALDH6A1 (14q24.1) | **Biochemical profile:** Moderately elevated urine methylmalonate<br>**Clinical features:** Developmental delay, seizures<br>**Treatment:** No effective treatment |
| Hyper-β-aminoisobutyric aciduria (210100) | D(R)-3-Aminoisobutyrate:pyruvate aminotransferase | Not determined | **Biochemical profile:** Elevated β-aminoisobutyric acid<br>**Clinical features:** Benign<br>**Treatment:** None needed |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Pyridoxine dependency with seizures (266100) | Not determined | Specific gene not determined (5q31.2-q31.3) | **Biochemical profile:** Elevated CSF glutamate<br>**Clinical features:** Seizure disorder refractory to conventional anticonvulsants, high-pitched cry, hypothermia, jitteriness, dystonia, hepatomegaly, hypotonia, dyspraxia, developmental delay<br>**Treatment:** Pyridoxine |
| GABA-transaminase deficiency (137150) | 4-Aminobutyrate-α-ketoglutarate aminotransferase | ABAT (16p13.3)* | **Biochemical profile:** Elevated plasma and CSF GABA and β-alanine, elevated carnosine<br>**Clinical features:** Accelerated linear growth, seizures, cerebellar hypoplasia, psychomotor delay, leukodystrophy, burst suppression EEG pattern<br>**Treatment:** No known treatment |
| 4-Hydroxybutyric aciduria (271980) | Succinic semialdehyde dehydrogenase | ALDH5A1 (6p22)* | **Biochemical profile:** Elevated urinary 4-hydroxybutyrate and glycine<br>**Clinical features:** Psychomotor retardation, speech delay, hypotonia<br>**Treatment:** Vigabatrin |
| Carnosinemia, homocarnosinosis, or both (236130, 212200) | Carnosinase | Specific gene not determined (18q21.3) | **Biochemical profile:** In carnosinemia phenotype, carnosinuria despite meat-free diet, elevated urine anserine after ingestion of food containing imidazole dipeptides, normal CSF<br>In homocarnosinosis phenotype, elevated CSF homocarnosine, normal serum carnosine<br>**Clinical features:** Usually benign; reported symptoms probably due to ascertainment bias<br>**Treatment:** None needed |
| **DISORDERS OF LYSINE METABOLISM** | | | |
| Hyperlysinemia (238700) | Lysine:α-ketoglutarate reductase | AASS (7q31.3)* | **Biochemical profile:** Hyperlysinemia<br>**Clinical features:** Muscle weakness, seizures, mild anemia, intellectual disability, joint and muscular laxity, ectopia lentis; sometimes benign<br>**Treatment:** Limited lysine intake |
| 2-Ketoadipic acidemia (245130) | 2-Ketoadipic dehydrogenase | Not determined | **Biochemical profile:** Elevated urine 2-ketoadipate, 2-aminoadipate, and 2-hydroxyadipate<br>**Clinical features:** Benign<br>**Treatment:** None needed |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Glutaric acidemia type I (231670) | Glutaryl CoA dehydrogenase | (19q13.2)* | **Biochemical profile:** Elevated urinary glutaric acid and 2-hydroxyglytaric acid<br>**Clinical features:** Dystonia, dyskinesia, degeneration of the caudate and putamen, frontotemporal atrophy, arachnoid cysts<br>**Treatment:** Aggressive treatment of intercurrent illness, carnitine<br>Protein, lysine, and tryptophan restriction possibly helpful |
| Saccharopinuria (268700) | α-Aminoadipic semialdehyde-glutamate reductase | AASS (7q31.3)* | **Biochemical profile:** Elevated urine lysine, citrulline, histidine, and saccharopine<br>**Clinical features:** Intellectual disability, spastic diplegia, short stature, EEG abnormality<br>**Treatment:** No clear treatment |
| **DISORDERS OF THE γ-GLUTAMYL CYCLE** | | | |
| γ-Glutamylcysteine synthetase deficiency (230450) | γ-Glutamylcysteine synthetase | GGLC (6p12)* | **Biochemical profile:** Aminoaciduria, glutathione deficiency<br>**Clinical features:** Hemolysis, spinocerebellar degeneration, peripheral neuropathy, myopathy<br>**Treatment:** No clear treatment; avoidance of drugs that trigger hemolytic crisis in G6PD deficiency |
| Pyroglutamic aciduria (5-oxoprolinuria; 266130, 231900) | Glutathione synthetase | GSS (20q11.2)* | **Biochemical profile:** Elevated urinary, plasma, and CSF 5-oxoproline; increased γ-glutamylcysteine; decreased glutathione level<br>**Clinical features:** Hemolysis, ataxia, seizures, intellectual disability, spasticity, metabolic acidosis<br>In mild form, no evidence of neurologic damage<br>**Treatment:** Na bicarbonate or citrate, vitamins E and C, avoidance of drugs that trigger hemolytic crisis in G6PD deficiency |
| γ-Glutamyltranspeptidase deficiency (glutathionuria; 231950) | γ-Glutamyltranspeptidase | Specific gene not determined (22q11.1-q11.2) | **Biochemical profile:** Elevated plasma and urinary glutathione<br>**Clinical features:** Intellectual disability<br>**Treatment:** No specific treatment |
| 5-Oxoprolinase deficiency (260005) | 5-Oxoprolinase | Not determined | **Biochemical profile:** Elevated urinary 5-oxoproline<br>**Clinical features:** Probably benign<br>**Treatment:** None needed |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| **DISORDERS OF HISTIDINE METABOLISM** | | | |
| Histidinemia (235800) | Classic: l-Histidine ammonia-lyase (liver and skin)<br>Variant: l-Histidine ammonia-lyase (liver only) | HAL (12q22-q23)* | **Biochemical profile:** Elevated plasma histidine<br>**Clinical features:** Frequently benign; neurologic manifestations in some patients<br>**Treatment:** Low-protein diet<br>For symptomatic patients only, controlled histidine intake |
| Urocanic aciduria (276880) | Urocanase | Not determined | **Biochemical profile:** Elevated urine urocanic acid<br>**Clinical features:** Probably benign<br>**Treatment:** None needed |
| **DISORDERS OF GLYCINE METABOLISM** | | | |
| Nonketotic hyperglycinemia (605899) | Glycine cleavage enzyme system<br>P protein<br>H protein<br>T protein<br>L protein | <br>GLDC (9p22)*<br>GCSH (16q23)*<br>ATM (3p21)*<br>Not determined | **Biochemical profile:** Elevated plasma and CSF glycine<br>**Clinical features:** In neonatal form, hypotonia, seizures, myoclonus, apnea, death<br>In infantile and episodic forms, seizures, intellectual disability, episodic delirium, chorea, vertical gaze palsy<br>In late-onset form, progressive spastic diplegia, optic atrophy, but no cognitive impairment or seizures<br>**Treatment:** No effective treatment; in some patients, temporary benefit from Na benzoate and dextromethorphan |
| **MISCELLANEOUS DISORDERS** | | | |
| Sarcosinemia (268900) | Sarcosine dehydrogenase | Specific gene not determined (9q34) | **Biochemical profile:** Elevated plasma sarcosine<br>**Clinical features:** Benign; intellectual disability reported<br>**Treatment:** None needed |
| D-Glyceric aciduria (220120) | D-Glycerate kinase | Not determined | **Biochemical profile:** Elevated urinary D-glyceric acid<br>**Clinical features:** Chronic acidosis, hypotonia, seizures, intellectual disability<br>**Treatment:** Bicarbonate or citrate for acidosis |
| Hartnup disorder (234500) | System B(0) neutral amino acid transporter | SLC6A19 (5p15)* | **Biochemical profile:** Neutral aminoaciduria<br>**Clinical features:** Atrophic glossitis, photodermatitis, intermittent ataxia, hypertonia, seizures, psychosis<br>**Treatment:** Nicotinamide |

## DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM—Continued

| DISEASE (OMIM NUMBER) | DEFECTIVE PROTEINS OR ENZYMES | DEFECTIVE GENE OR GENES (CHROMOSOMAL LOCATION) | COMMENTS |
|---|---|---|---|
| Cystinuria | Renal dibasic amino acid transporter | — | **Biochemical profile:** Elevated urinary cystine, lysine, arginine, and ornithine |
| Type I (220100) | Heavy subunit | SLC3A1 (2p16.3)* | **Clinical features:** Nephrolithiasis, increased risk of impaired cerebral function |
| Types II and III (600918) | Light subunit | SLC7A9 (19q13.1)* | **Treatment:** Maintenance of fluid intake, bicarbonate or citrate, penicillamine or mercaptopropionylglycine |
| Iminoglycinuria (242600) | Renal transporter of proline, hydroxyproline, and glycine | Not determined | **Biochemical profile:** Elevated urinary proline, hydroxyproline, and glycine but normal plasma levels<br>**Clinical features:** Probably benign<br>**Treatment:** None needed |
| Guanidinoacetate methyltransferase deficiency (601240) | Guanidinoacetate methyltransferase | GAMT (19p13.3)* | **Biochemical profile:** Elevated guanidinoacetate, decreased creatine and phosphocreatine<br>**Clinical features:** Developmental delay, hypotonia, extrapyramidal movements, seizures, autistic behavior<br>**Treatment:** Creatine supplementation |
| Cystinosis | See Table Disorders of Purine and Pyrimidine Metabolism | | |

*Gene has been identified, and molecular basis has been elucidated.

OMIM = online mendelian inheritance in man (see database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).