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			
Transient tyrosinemia	4-Hydroxyphenylpyruvate dioxygenase	Not genetic	**Biochemical profile:** Elevated plasma phenylalanine and tyrosine **Clinical features:** Usually occurring in premature infants; mostly asymptomatic Occasionally poor feeding and lethargy **Treatment:** Tyrosine restriction and ascorbate supplementation for symptomatic patients only

Disorders of branched-chain amino acid (valine, leucine, isoleucine) metabolism			
Propionic acidemia (606054)	Propionyl-CoA carboxylase		**Biochemical profile:** Elevated plasma glycine, urine methylcitrate, 3-hydroxypropionate, propionylglycine, and tiglylglycine **Clinical features:** Hypotonia, vomiting, lethargy, coma, ketoacidosis, hypoglycemia, hyperammonemia, bone marrow suppression, growth delay, intellectual disability, physical disability **Treatment:** During acute episodes, high-dose glucose and aggressive fluid resuscitation For extreme hyperammonemia, may need hemodialysis or peritoneal dialysis 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)
Type I	α-Subunit	PCCA (13q32)*	
Type II	β-Subunit	PCCB (3q21-q22)*	

Methylmalonic acidemia (mut defects; 251000)	Methylmalonyl-CoA mutase Mut0 (no enzyme activity) Mut- (some residual enzyme activity)	MUT (6p21)*	**Biochemical profile:** Elevated plasma glycine; increased urine methylmalonate, 3-hydroxypropionate, methylcitrate, and tiglylglycine **Clinical features:** Hypotonia, vomiting, lethargy, coma, ketoacidosis, hypoglycemia, hyperammonemia, bone marrow suppression, growth delay, intellectual disability, and physical disability **Treatment:** During acute episodes, high-dose glucose and aggressive fluid resuscitation For extreme hyperammonemia, may need hemodialysis or peritoneal dialysis For long-term management, controlled intake of threonine, valine, isoleucine, and methionine; carnitine supplementation; vitamin B_{12} for patients with mut- type
Isovaleric acidemia (243500)	Isovaleryl-CoA dehydrogenase	IVD(15q14-q15)*	**Biochemical profile:** Isovaleryl glycine, 3-hydroxyisovalerate **Clinical features:** Characteristic sweaty feet odor, vomiting, lethargy, acidosis, intellectual disability, bone marrow suppression, hypoglycemia; ketoacidosis, hyperammonemia, neonatal death **Treatment:** Controlled leucine intake, glycine, carnitine

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 **Clinical features:** Reye-like syndrome, vomiting, hypotonia, acidosis, hypoglycemia, lethargy, hyperammonemia without ketosis **Treatment:** Restricted leucine intake, control of hypoglycemia
2-Methylbutyryl glycinuria (600301)	Short branched-chain acyl-CoA dehydrogenase	ACADSB (10q25-q26)*	**Biochemical profile:** Elevated urine 2-methylbutyrulglycine **Clinical features:** Hypotonia, muscular atrophy, lethargy, hypoglycemia, hypothermia **Treatment:** No effective treatment

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 **Clinical features:** In males, recurrent vomiting, irritability, lethargy, hyperammonemic coma, cerebral edema, spasticity, intellectual disability, seizures, death 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 **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)

Citrullinemia type I (215700)	Argininosuccinic acid synthetase	ASS (9q34)*	**Biochemical profile:** High plasma citrulline and glutamine, citrullinuria, orotic aciduria **Clinical features:** Episodic hyperammonemia, growth failure, protein aversion, lethargy, vomiting, coma, seizures, cerebral edema, developmental delay **Treatment:** Similar to that for OTC deficiency except citrulline supplementation is not recommended
Argininosuccinic aciduria (207900)	Argininosuccinate lyase	ASL (7cen-q11.2)*	**Biochemical profile:** Elevated plasma citrulline and glutamine, elevated urine argininosuccinate **Clinical features:** Episodic hyperammonemia, hepatic fibrosis, elevated liver enzymes, hepatomegaly, protein aversion, vomiting, seizures, intellectual disability, ataxia, lethargy, coma, trichorrhexis nodosa **Treatment:** Arginine supplementation

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http://www.merckmanuals.com/professional/pediatrics/inherited_disorders_of_metabolism/amino_acid_and_organic_acid_metabolism_disorders.html