435e Inherited Defects of Membrane Transport

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Specific membrane transporters mediate the passage of a wide variety of substances across cellular membranes. Classes of substrates include amino acids, sugars, cations, anions, vitamins, and water. The number of inherited disorders of membrane transport continues to increase with the identification of new transporters on the plasma membrane or intracellular organelles and the clarification of the molecular basis of diseases with previously unknown pathophysiology. The first transport disorders identified affected the gut or the kidney, but transport processes are now proving essential for the normal function of every organ. Mutations in transporter molecules cause disorders of the heart, muscle, brain, and endocrine and sensory organs (Table 435e-1). Inherited defects impairing the transport of selected amino acids that can present in adults are discussed here as examples of the abnormalities encountered; others are considered elsewhere in this text.

CYSTINURIA

Cystinuria (frequency of 1 in 10,000 to 1 in 15,000) is an autosomal recessive disorder caused by defective transporters in the apical brush border of proximal renal tubule and small intestinal cells. It is characterized by impaired reabsorption and excessive urinary excretion of the dibasic amino acids lysine, arginine, ornithine, and cystine. Because cystine is poorly soluble, its excess excretion predisposes to the formation of renal, ureteral, and bladder stones. Such stones are responsible for the signs and symptoms of the disorder.

There are two variants of cystinuria. Homozygotes for both variants have high urinary excretion of cystine, lysine, arginine, and ornithine. Type I heterozygotes usually have normal urinary amino acid excretion, whereas most non–type I (formerly type II and type III) heterozygotes have moderately increased urinary excretion of each of the four amino acids. The gene for type I cystinuria (*SLC3A1*, chromosome 2p16.3) encodes a membrane glycoprotein. Non–type I cystinuria is caused by mutations in *SLC7A9* (chromosome 19q13) that encodes the $b^{0,+}$ amino acid transporter. The glycoprotein encoded by *SLC3A1* favors the correct processing of the $b^{0,+}$ membrane transporter and explains why mutations in two different genes cause a similar disease.

TABLE 435e-1 GENETIC DISORDERS OF MEMBRANE TRANSPORT (SELECTED EXAMPLES)

Class of Substance and Disorder	Individual Substrates	Tissues Manifesting Transport Defect	Molecular Defect	Major Clinical Manifestations	Inheritance
Amino Acids					
Cystinuria	Cystine, lysine, arginine, ornithine	Proximal renal tubule, jejunal mucosa	Shared dibasic-cystine transporter *SLC3A1, SLC7A9*	Cystine nephrolithiasis	AR
Dibasic aminoaciduria	Lysine, arginine, ornithine	Proximal renal tubule, jejunal mucosa	Dibasic transporter *SLC7A7*	Protein intolerance, hyperammonemia, intellectual disability	AR
Hartnup disease	Neutral amino acids	Proximal renal tubule, jejunal mucosa	Neutral amino acid transporter *SLC6A19*	Constant neutral aminoaciduria, intermittent symptoms of pellagra	AR
Citrullinemia type 2	Aspartate, glutamate, malate	Inner mitochondrial membrane	Mitochondrial aspartate/glutamate carrier 2 *SLC25A13*	Sudden behavioral changes with stupor, coma, hyperammonemia	AR
Hyperornithinemia, hyperammonemia, homocitrullinuria	Ornithine, citrulline	Inner mitochondrial membrane	Mitochondrial ornithine carrier *SLC25A15*	Vomiting, lethargy, failure to thrive, intellectual disability, episodic confusion, hyperammonemia, protein intolerance	AR
Histidinuria	Histidine	Proximal renal tubule, jejunal mucosa	Histidine transporter	Intellectual disability	AR
Iminoglycinuria	Glycine, proline, hydroxyproline	Proximal renal tubule, jejunal mucosa	Shared glycine–imino acid transporter *SLC36A2, SLC6A19, SLC6A20*	None	AR
Dicarboxylic aminoaciduria	Glutamic acid, aspartic acid	Proximal renal tubule, jejunal mucosa	Shared dicarboxylic amino acid transporter	None	Probable AR
Cystinosis	Cystine	Lysosomal membranes	Lysosomal cystine transporter	Renal failure, hypothyroidism, blindness	AR
Hexoses					
Glucose-galactose malabsorption	D-Glucose D-Galactose	Proximal renal tubule, jejunal mucosa	Sodium-dependent glucose/galactose transporter SGLT1	Watery diarrhea on feeding glucose, lactose, sucrose, or galactose	AR
Glucose-transport defect	D-Glucose	Ubiquitous blood-brain barrier	Facilitative glucose transporter GLUT1	Seizures, intellectual disability	AD
Fanconi-Bickel syndrome	D-Glucose	Liver, kidney, pancreas, intestine	Facilitative glucose transporter GLUT2	Growth retardation, rickets, hepatorenal glycogenosis, hypo- and hyperglycemia	AR
Urate					
Hypouricemia	Uric acid	Proximal renal tubule	Urate transporter *SLC22A12*	Hypouricemia, uric acid urolithiasis	AR
Vitamins					
Thiamine-responsive megaloblastic anemia	Thiamine	Ubiquitous	Thiamine transporter *SLC19A2*	Megaloblastic anemia, deafness, diabetes mellitus	AR
Other					
Carnitine deficiency	Carnitine	Kidney, muscle, heart	Carnitine transporter OCTN2	Hypoketotic hypoglycemia, cardiomyopathy, sudden death	AR
Creatine deficiency	Creatine	Brain	Creatine transporter *SLC6A8*	Intellectual disability, seizures, hypotonia	XL

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked recessive.