TABLE 332e-1 INHERITED DISORDERS AFFECTING RENAL TUBULAR ION AND SOLUTE TRANSPORT

Disease or Syndrome	Gene	OMIM[a]
Disorders Involving the Proximal Tubule		
Proximal renal tubular acidosis	Sodium bicarbonate cotransporter (*SLC4A4*, 4q21)	604278
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (*SLC2A2*, 3q26.2)	227810
Isolated renal glycosuria	Sodium glucose cotransporter (*SLC5A2*, 16p11.2)	233100
Cystinuria		
Type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1*, 2p16.3)	220100
Non-type I	Amino acid transporter, light subunit (*SLC7A9*, 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7*, 4q11.2)	222700
Hartnup disorder	Neutral amino acid transporter (*SLC6A19*, 5p15.33)	34500
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (*SLC34A3*, 9q34)	241530
Renal hypouricemia		
Type 1	Urate-anion exchanger (*SLC22A12*, 11q13)	220150
Type 2	Urate transporter, GLUT9 (*SLC2A9*, 4p16.1)	612076
Dent disease	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter syndrome		
Type 1	Sodium, potassium chloride cotransporter (*SLC12A1*, 15q21.1)	241200
Type 2	Potassium channel, ROMK (*KCNJ1*, 11q24)	601678
Type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.33))	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman syndrome	Sodium chloride cotransporter (*SLC12A3*, 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B*, *SCNN1G*, 16p12.1)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, a, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B*, *SCNN1G*, 16pp12.1)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (*AQP2*, 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (*SLC4A1*, 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (*SLC4A1*, 17q21.31)	602722
with neural deafness	Proton ATPase, β1 subunit (*ATP6V1B1*, 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (*ATP6V0A4*, 7q34)	602722

[a]Online Mendelian Inheritance in Man database (*http://www.ncbi.nlm.nih.gov/Omim*).

This process is saturable, resulting in urinary bicarbonate excretion when plasma levels exceed the physiologically normal range (24-26 meq/L). Carbonic anhydrase inhibitors such as acetazolamide, a class of weak diuretic agents, block proximal tubule reabsorption of bicarbonate and are useful for alkalinizing the urine.

The proximal tubule contributes to acid secretion by two mechanisms involving the titration of the urinary buffers ammonia (NH_3) and phosphate. Renal NH_3 is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH_3 out of the proximal tubular cell enables trapping of H^+ secreted by sodium-proton exchange in the lumen as ammonium ion (NH_4^+). Cellular K^+ levels inversely modulate proximal tubular ammoniagenesis, and in the setting of high serum K^+ from hypoaldosteronism, reduced ammoniagenesis facilitates the appearance of type IV renal tubular acidosis.

Filtered hydrogen phosphate ion (HPO_4^{2-}) is also titrated in the proximal tubule by secreted H^+ to form $H_2PO_4^-$, and this reaction constitutes a major component of the urinary buffer referred to as titratable acid. Most filtered phosphate ion is reabsorbed by the proximal tubule through a sodium-coupled cotransport process that is regulated by parathyroid hormone.

Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in Cl^- concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proximal tubular segments, cellular Cl^- reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of Cl^-. Once in the lumen, formate anions are titrated by H^+ (provided by Na^+/H^+ exchange) to generate neutral formic acid, which can diffuse passively across the apical membrane back into the cell where it