Physiol Rev 99: 1575–1653, 2019
Published June 19, 2019; doi:10.1152/physrev.00008.2018

LEARNING PHYSIOLOGY FROM INHERITED KIDNEY DISORDERS

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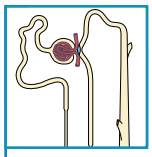


van der Wijst J, Belge H, Bindels RJM, Devuyst O. Learning Physiology From Inherited Kidney Disorders. *Physiol Rev* 99: 1575–1653, 2019. Published June 19, 2019; doi:10.1152/physrev.00008.2018.—The identification of genes causing inherited kidney diseases yielded crucial insights in the molecular basis of disease and improved our understanding of physiological processes that operate in the kidney. Monogenic kidney disorders are caused by mutations in genes coding for a large variety of proteins including receptors, channels and transporters, enzymes, transcription factors, and structural components, operating in specialized cell types that perform highly regulated homeostatic functions. Common variants in some of these genes are also associated with complex traits, as evidenced by genome-wide association studies in the general population. In this review, we discuss how the molecular genetics of inherited disorders affecting different tubular segments of the nephron improved our understanding of various transport processes and of their involvement in homeostasis, while providing novel therapeutic targets. These include inherited disorders causing a dysfunction of the proximal tubule (renal Fanconi syndrome), with emphasis on epithelial differentiation and receptor-mediated endocytosis, or affecting the reabsorption of glucose, the handling of uric acid, and the reabsorption of sodium, calcium, and magnesium along the kidney tubule.

I. INTRODUCTION: GENETICS OF KIDNEY DISORDERS

Over the past 25 yr, identification of the genetic variants causing inherited kidney diseases has tremendously enhanced our understanding of the molecular basis of disease, allowing to identify new therapeutic targets susceptible to alleviate disease onset or progression (159, 779). At the same time, these genetic discoveries have been a dominant force in the field of renal physiology, providing clues for a number of essential functions that were previously unknown or only postulated on the basis of classical experimental approaches (see BOX 1).

The clustering of kidney disease in families has long been recognized (184). From the 1980s, the technique of linkage analysis allowed to map a number of major disorders, including autosomal dominant polycystic kidney disease (ADPKD) to chromosome 16 in 1985 (595). This was followed by positional cloning, which allowed to identify disease-causing mutations in genes involved in "monogenic" or "Mendelian" diseases affecting various segments of the nephron, such as Alport syndrome (32), nephrogenic diabetes insipidus (624), ADPKD type 1 (739a), Liddle syndrome (686), Dent disease (439), Bartter and Gitelman syndromes (691, 694), cystinosis (748), and steroid-resistant nephrotic syndrome (72). With the emergence of next-generation sequencing (NGS) technologies (i.e., whole exome and whole genome sequencing), the identification of gene defects causing inherited kidney disorders is expected to increase rapidly. To date, more than 160 rare kidney diseases have been defined, with an overall prevalence of ~60–80 cases per 100,000 total population in Europe and the United States (US) (159). Classically, a disease is defined as "rare" if it affects <200,000 persons in the US, or <1 in 2,000 people in Europe (654). At least 10% of adults and nearly all children who progress to renal replacement therapy have an inherited kidney disease; collectively, the latter represent the fifth most common cause of end-stage renal disease (ESRD) after diabetes, hypertension, glomerulonephritis, and pyelonephritis (159).

The monogenic disorders of the kidney are caused by mutations in genes coding for a large variety of proteins including receptors, channels and transporters, enzymes, transcription factors, and structural components. Since the kidney is a complex organ involving numerous specialized cell types performing highly regulated homeostatic functions (184), these disorders often affect vital processes including water and electrolyte balance, blood pressure regulation, acid-base homeostasis, tis-

sue oxygen supply, hormone and vitamin metabolism, growth and puberty, innate and adaptive immunity, metabolic clearance and secretion of drug metabolites, and central nervous and cognitive functions. Thanks to the progress in renal replacement therapy (i.e., dialysis and transplantation), patients with inherited kidney disorders rarely die when their disease progresses. However, this apparent advantage is counterbalanced by compromised health with poor quality of life. For instance, children born with severe congenital nephropathies, who can be dialyzed from neonatal age onwards, face many decades of life with ESRD and high likelihood of altered physical, cognitive, and psychosocial development. Inherited kidney disorders have multi-systemic complications (27, 159).

BOX 1.

- The review discusses how identification of genes causing inherited tubulopathies yielded crucial insights in physiological processes that operate in the kidney tubule.
- The genes involved code for receptors, channels and transporters, enzymes, transcription factors, and structural components.
- This article specifically addresses genetic disorders causing proximal tubule dysfunction (renal Fanconi syndrome) or affecting the reabsorption of glucose, the handling of uric acid, and the reabsorption of sodium, calcium, and magnesium.
- Each section summarizes the physiology process, the clinical manifestations and genetics of the disease, the mechanistic insights, and the therapeutic perspectives.

In addition to monogenic renal diseases, there is strong evidence for a genetic (heritable) component to various aspects of renal function ranging from the glomerular filtration rate (GFR) to the tubular handling of ions and the susceptibility to chronic kidney disease (CKD) or hypertension. Classic twin studies demonstrated heritabilities between 40 and 50% for the tubular handling of major ions, and up to 63% for calculated creatinine clearance (327). A recent, population-based approach evidenced significant heritability values for the 24-h fractional excretions of common electrolytes, ranging from 16% for potassium (K^+) to 51% for calcium (Ca^{2+}) in the general adult population (500). The identification of the genetic component of such complex multi-factorial traits requires unbiased genome-wide mapping approaches such as genome-wide association studies (GWAS), which have emerged since the mid 2000s (828). These studies have been very successful at identifying genomic regions associated with estimated GFR (eGFR) (102, 407) and albuminuria (75) as well as CKD in the general population (553). As for other complex diseases, the identified genetic risk variants only confer relatively small increases in disease risk, with identification requiring large study populations (163). It should be pointed out, however, that the border between monogenic and complex genetic disorders is evolving, as an increasing number of GWAS based on defined traits and large populations is evidencing loci that contain genes involved in monogenic disorders (828). These findings, which are verified for traits related to eGFR, albumin excretion, and tubular handling of electrolytes (74, 133, 134, 553) support the existence of a continuum of risk variants in important genes that are associated with physiological variation in the general population (frequent variants, small effect size) and also involved in Mendelian disorders (rare variants, large effect size) (116, 456) **(FIGURE 1)**.

II. FOCUS OF THE REVIEW

The advent of genetic technologies and the rapid increase in the identification of genes causing inherited kidney disorders or associated with complex renal traits provided unprecedented insights into basic principles operating in different nephron segments. In turn, these insights improved our understanding of important transport mechanisms, their regulation, and their involvement in homeostatic processes, and they provided novel therapeutic targets. These discoveries were facilitated by large-scale international research consortia focusing on rare genetic disorders and were amplified by large collaborative studies for GWAS and subsequent mechanistic investigations (159, 161, 406, 441, 553, 812).

In this review, we discuss inherited disorders affecting different tubular segments **(TABLE 1; FIGURE 2)**, with emphasis on those that yielded critical insights for the understanding of epithelial transport processes. The review focuses on inherited disorders causing a dysfunction of the proximal tubule (renal Fanconi syndrome) which evidenced the role of epithelial differentiation and receptor-mediated endocytosis in multi-systemic complications and progression of renal disease; affecting glucose transport and uric acid handling; disturbing the renal handling of Na^+, with direct relevance for blood pressure regulation and mechanisms of action of diuretics; and affecting the handling of Ca^{2+} and Mg^{2+}. Disorders affecting acid-base balance, phosphate handling and its hormonal regulation (7, 43, 52, 321, 460, 549, 714, 783, 788, 802) and water handling (31, 61, 126, 403, 543, 637, 807) have been discussed in recent reviews and will not be addressed here. In each section, we summarize the specific physiology process, discuss the clinical manifestations and genetics of the associated inherited disorders, and detail the mechanistic insights and therapeutic perspectives provided by these studies.

III. RARE INHERITED DISORDERS HIGHLIGHTING TUBULAR FUNCTIONS

A. Proximal Tubule Dysfunction: Renal Fanconi Syndrome

1. Receptor-mediated endocytosis and endolysosomal compartment

The proximal tubule (PT) plays an essential role in the reabsorption and processing of a large amount of filtered ions

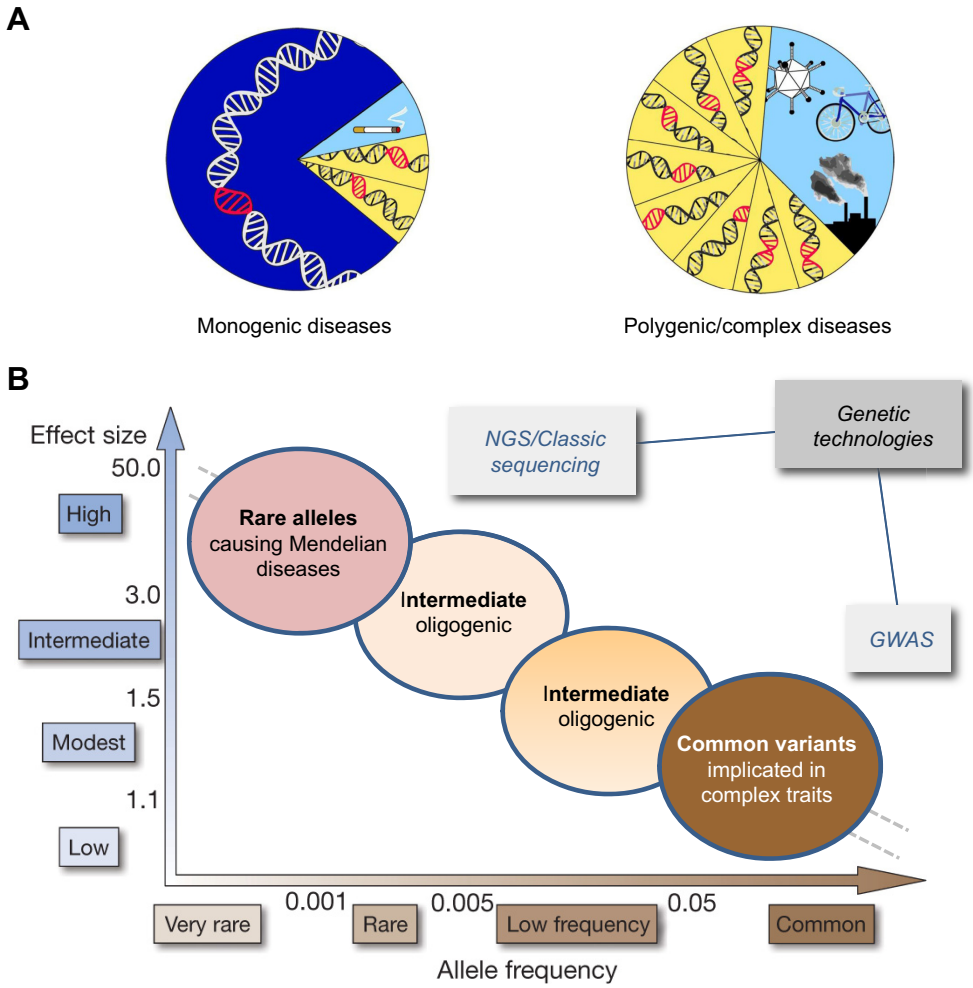


FIGURE 1. Genetic influence on disease. *A*: disorders with a genetic component are classically divided between monogenic diseases, in which a rare variant in a single gene is the main cause of the disease (dark blue sector), with possible additional, minor contributions of modifier genes (yellow sectors) and environment (light blue sector); and polygenic/complex diseases, where many variants each exerting a very small effect (yellow sectors), combined with a strong set of environmental factors (blue sector) contribute to disease. Oligogenic disorders are caused by, or modulated by, a few genes. *B*: the spectrum of genetic influence on disease can be represented by an inverse relationship between the strength of genetic effect (effect size) and the allele frequency in the population. Rare disease-associated allelic variants (typically, <1:2,000 individuals) are involved in Mendelian disorders, whereas common variants (typically >5% in the population) with small effect size contribute to complex traits. Genetic variants of intermediate effect-size contribute to polygenic disorders. Genetic technologies, including next-generation sequencing (NGS) and genome-wide association studies (GWAS), cover the spectrum. [Adapted from Manolio et al. (455) and Manolio et al. (456).]

and solutes. Approximately two-thirds of the filtered water, NaCl, Ca^{2+} as well as the totality of glucose, phosphate, amino acids are reabsorbed by a whole orchestra of specialized transport systems that operate on the apical (brush border) and basolateral area of the cells lining the various segments of the PT, driven by the electrochemical gradient generated by the basolateral Na^+-K^+-ATPase. These transport processes impose a high energy demand, which is sustained by numerous, elongated mitochondria typically identified in PT cells (408). In addition, PT cells also reabsorb a significant amount of albumin (66.5 kDa) and low-molecular-weight (LMW) plasma proteins that are filtered through the glomerular basement membrane. These LMW proteins include hormones [e.g., parathyroid hormone (PTH), insulin, epidermal growth factor, leptin, thyroglobulin], vitamin carrier proteins (transcobalamin-vitamin B_{12}, vitamin D-binding protein (DBP), retinol-binding protein, folate-binding protein), enzymes (e.g., cathepsin B, α-amylase, plasminogen, urokinase, lysozyme), lipoproteins, cell surface antigen components (β_2-microglobulin), immunoglobulin light chains, as well as drugs and toxins (e.g., aminoglycosides, gentamicin). As the majority of the LMW proteins are reabsorbed and metabolized by the PT cells, the human urine is virtually devoid of plasma proteins under physiological conditions (120, 194, 519).

The uptake of albumin and LMW proteins by PT cells principally involves receptor-mediated, clathrin-dependent en-

Table 1. *Rare inherited tubular disorders highlighting tubular functions*

	Transmission	MIM Number	Gene (Location)	Defective Protein	Protein Function
Proximal tubule dysfunction: renal Fanconi syndrome					
Donnai-Barrow syndrome (Faciooculoacousticorenal syndrome)	AR	222448	*LRP2 (2q31.1)*	Megalin	Low-density lipoprotein receptor-related protein 2, multiligand receptor
Imerslund-Gräsberck syndrome megaloblastic anemia 1, Finnish type	AR	261100	*CUBN (10p13)*	Cubilin	Multiligand receptor (including intrinsic factor-vitamin B_{12})
Imerslund-Gräsberck syndrome megaloblastic anemia 1, Norwegian type	AR	261100	*AMN (14q32.32)*	Amnionless	Partner of cubilin, directs subcellular localization of cubilin
Dent disease 1 (nephrolithiasis, hypercalciuric, *X*-linked)	XL	300009	*CLCN5 (Xq11.23)*	ClC-5	$2Cl^-/H^+$ exchanger
Dent disease 2	XL	300555	*OCRL (Xq26.1)*	OCRL	Inositol polyphosphate 5-phosphatase
Lowe oculocerebrorenal syndrome	XL	309000	*OCRL*	OCRL	Inositol polyphosphate 5-phosphatase
Cystinosis, nephropathic	AR	219800	*CTNS (17p13.2)*	Cystinosin	Lysosomal cystine-H^+ cotransporter
Cystic fibrosis	AR	219700	*CFTR (7q31.2)*	CFTR	ATP-binding cassette (ABC) transporter, Cl^- channel
Maturity-onset diabetes of the young, type 3 (MODY3)	AD	600496	*HNF1A (12q24.31)*	HNF1α	Transcription factor
Disorders of uric acid handling					
Renal hypouricemia type 1	AR	220150	*SLC22A12 (11q13.1)*	URAT1	Urate/anion exchanger
Renal hypouricemia type 2	AR	612076	*SLC2A9 (4p16.1)*	GLUT9	Facilitated glucose transporter, urate transporter
Disorders of glucose transport					
Familial renal glycosuria	AR/AD	233100	*SLC5A2 (16p11.2)*	SGLT2	Sodium/glucose cotransporter
Glucose/galactose malabsorption	AR	606824	*SLC5A1 (22q12.3)*	SGLT1	Sodium/glucose cotransporter
Fanconi-Bickel syndrome (hepatorenal glycogenosis)	AR	227810	*SLC2A2 (3q26.2)*	GLUT2	Facilitated glucose transporter
Disorders of sodium chloride transport					
Bartter syndrome type 1 (hypokalemic alkalosis with hypercalciuria 1, antenatal)	AR	601678	*SLC12A1 (15q21.1)*	NKCC2	Na^+-K^+-$2Cl^-$ cotransporter
Bartter syndrome type 2 (hypokalemic alkalosis with hypercalciuria 2, antenatal)	AR	241200	*KCNJ1 (11q24.3)*	ROMK	K^+ channel (renal outer-medullary K^+ channel)
Bartter syndrome type 3 (with hypocalciuria)	AR	607364	*CLCNKB (1p36.13)*	ClC-Kb	Cl^- channel
Bartter syndrome type 4 (neonatal, with sensorineural deafness)	AR	602522	*BSND (1p32.3)*	Barttin	Subunit of the ClC-Ka and ClC-Kb channels
Bartter syndrome type 4b, digenic (neonatal, with sensorineural deafness)	AR	613090	*CLCNKA (1p36.13), CLCNKB*	ClC-Ka; ClC-Kb	Cl^- channel; Cl^- channel
Gitelman syndrome (hypomagnesemia-hypokalemia, primary renotubular, with hypocalciuria)	AR	263800	*SLC12A3 (16q13)*	NCC	Thiazide-sensitive Na^+-Cl^- cotransporter
Pseudohypoaldosteronism type IIC (Gordon syndrome)	AD	614492	*WNK1 (12p13.33)*	WNK1	Ser/Thr kinase modulating Na^+- and K^+-coupled Cl^- transporters
Pseudohypoaldosteronism type IIB	AD	614491	*WNK4 (17q21.2)*	WNK4	Ser/Thr kinase modulating Na^+- and K^+-coupled Cl^- transporters
Pseudohypoaldosteronism type IID	AD	614495	*KLHL3 (5q31.2)*	KLHL3	Substrate adaptor for cullin-3
Pseudohypoaldosteronism type IIE	AD	614496	*CUL3 (2q36.2)*	Cullin-3	Component of ubiquitin E3 ligase complex
Liddle syndrome (pseudohyperaldosteronism)	AD	177200	*SCNN1G (16p12.2), SCNN1B (16p12.2)*	ENaC	γ-Subunit of amiloride-sensitive Na^+ channel; β-subunit of amiloride-sensitive Na^+ channel
Pseudohypoaldosteronism type I	AD	177735	*NR3C2 (4q31.23)*	MR	Mineralocorticoid receptor
	AR	264350	*SCNN1A (12p13.31), SCNN1G, SCNN1B*	ENaC	α-Subunit of amiloride-sensitive Na^+ channel; γ-subunit of amiloride-sensitive Na^+ channel; β-subunit of amiloride-sensitive Na^+ channel

Continued

Table 1.—*Continued*

	Transmission	MIM Number	Gene (Location)	Defective Protein	Protein Function
Disorders of calcium transport					
Familial hypocalciuric hypercalcemia, type 1	AD	145980	*CASR (3q13.3-q21.1)*	CaSR	Calcium-sensing receptor
Familial hypocalciuric hypercalcemia, type 2	AD	145981	*GNA11 (19p13.3)*	$G\alpha_{11}$	Guanine nucleotide-binding protein, G protein subunit α11
Familial hypocalciuric hypercalcemia, type 3	AD	600740	*AP2S1 (19q13.32)*	AP2S1	Adaptor-related protein complex 2, sigma-1 subunit
Neonatal severe hyperparathyroidism	AR	239200	*CASR*	CaSR	Calcium-sensing receptor
Autosomal dominant hypocalcemia 1 (with Bartter syndrome)	AD	601198	*CASR*	CaSR	Calcium-sensing receptor
Autosomal dominant hypocalcemia 2	AD	615361	*GNA11*	$G\alpha_{11}$	Guanine nucleotide-binding protein, G protein subunit α11
Disorders of magnesium transport					
Hypomagnesemia (intestinal, type 1)	AR	602014	*TRPM6 (9q21.13)*	TRPM6	Mg^{2+} channel
Hypomagnesemia (renal, type 2)	AD	154020	*FXYD2 (11q23.3)*	FXYD2	γ-Subunit of Na^{+}-K^{+}-ATPase
Hypomagnesemia (renal, type 3)	AR	248250	*CLDN16 (3q28)*	Claudin-16	Paracellular protein, component of tight junctions
Hypomagnesemia (renal, type 4)	AR	611718	*EGF (4q25)*	EGF	Epidermal growth factor
Hypomagnesemia (renal, type 5) with ocular involvement	AR	248190	*CLDN19 (1p34.2)*	Claudin-19	Paracellular protein, component of tight junctions
Hypomagnesemia (renal, type 6)	AD	613882	*CNNM2 (10q24.32)*	Cyclin M2	Membrane protein of unknown function
Hypomagnesemia, seizures, and mental retardation	AR, AD	616418	*CNNM2*	Cyclin M2	Membrane protein of unknown function
HELIX syndrome (hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia)	AR	617671	*CLDN10 (13q32.1)*	Claudin-10	Paracellular protein, component of tight junctions
SeSAME (or EAST) syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)	AR	612780	*KCNJ10 (1q23.2)*	Kir4.1	K^{+} channel
Renal cysts and diabetes syndrome	AD	137920	*HNF1B (17q12)*	HNF1β	Transcription factor

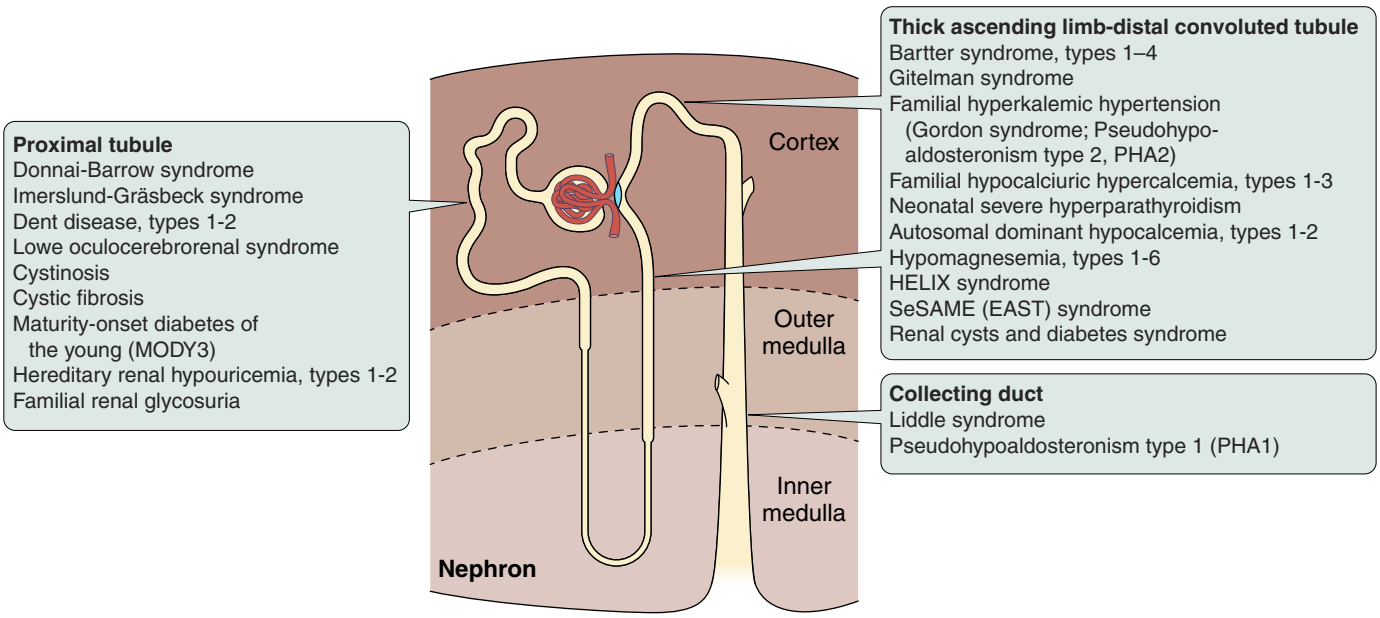


FIGURE 2. Segmental distribution of rare inherited kidney disorders. See text for details on the individual disorders.

docytosis **(FIGURE 3)**, which requires two multiligand receptors, megalin and cubilin, and the cooperating protein amnionless (AMN). These proteins are expressed at the brush border of the PT cells, with megalin showing a maximal expression level in the S1 versus S2 and S3 segments (194, 520). Megalin is a member of the low-density lipoprotein receptor (LDLR) family, whereas cubilin (also known as the intestinal intrinsic factor-vitamin B_{12} receptor) is a highly conserved membrane-associated protein with little structural homology to known endocytic receptors and is characterized by the absence of a transmembrane domain. Megalin seems to be involved in the endocytosis and intracellular trafficking of cubilin as suggested by the high-affinity binding of purified megalin to cubilin amino (NH_2)-terminal region in vitro (120). AMN is required for the apical sorting of cubilin and its participation in receptor-mediated endocytosis (136). Cubilin contributes ligand-binding regions of the receptor complex, whereas AMN ensures the membrane anchorage, biosynthetic processing, and recycling of the complexes at the plasma membrane (224). In addition to the proximal tubule, cubilin and amnionless are both expressed in the small intestine. Ligand binding and interactions between both receptors induce their internalization into coated vesicles and their subsequent delivery to endosomes and lysosomes for ligand processing and receptor degradation or recycling.

Through its binding capacity of hedgehog morphogens, megalin modulates sonic hedgehog activities crucial for developmental processes in a number of tissues, including the brain, the eye, and the heart (117). The biological importance of the apical receptor complex is evidenced by the severe and multi-sytemic manifestations of rare disorders targeting megalin and cubilin/amnionless **(FIGURE 4)**. Recessive mutations in the *LRP2* gene that encodes megalin cause Donnai-Barrow or facio-oculo-acoustico-renal (DB/FOAR) syndrome (MIM no. 222448) that is characterized by typical craniofacial anomalies (major hypertelorism with bulging eyes), high-grade myopia, deafness and LMW proteinuria (369, 712). Mutations in the *CUBN* and *AMN* genes that encode cubilin and amnionless, respectively, are associated with Imerslund-Gräsbeck syndrome (MIM no. 261100), a rare autosomal recessive disorder characterized by selective vitamin B_{12} (cobalamin) malabsorption causing megaloblastic anemia. Increased urinary excretion of cubilin ligands (e.g., transferrin, DBP, and albumin) is detected in patients harbouring mutations impairing the plasma membrane expression of cubilin (713). Recent studies have demonstrated that the apical expression of megalin, and thus the endocytic uptake capacity, reflects the differentiation state of PT cells. For instance, comparison of proliferation and differentiation markers revealed that primary human PT cells are less proliferative and more differentiated than HK-2 cells, reflected by a threefold increase in their endocytic uptake (578). These results are in line with studies demonstrating that primary cultured cells isolated from PT segments of mouse kidney preserve their differentiation and polarized transport processes (738). Furthermore, acquired PT dysfunction (e.g., by exposing PT cells to low dose of toxic κ-light chains) is inducing a phenotype switch of PT cells, with increased cell proliferation, decreased apical expression of endocytic receptors, and defective endocytosis and albumin uptake capacity (449).

The progression along the endolysosomal compartment depends on the continuous vesicular acidification from early endosomes to lysosomes (199). The decrease in pH

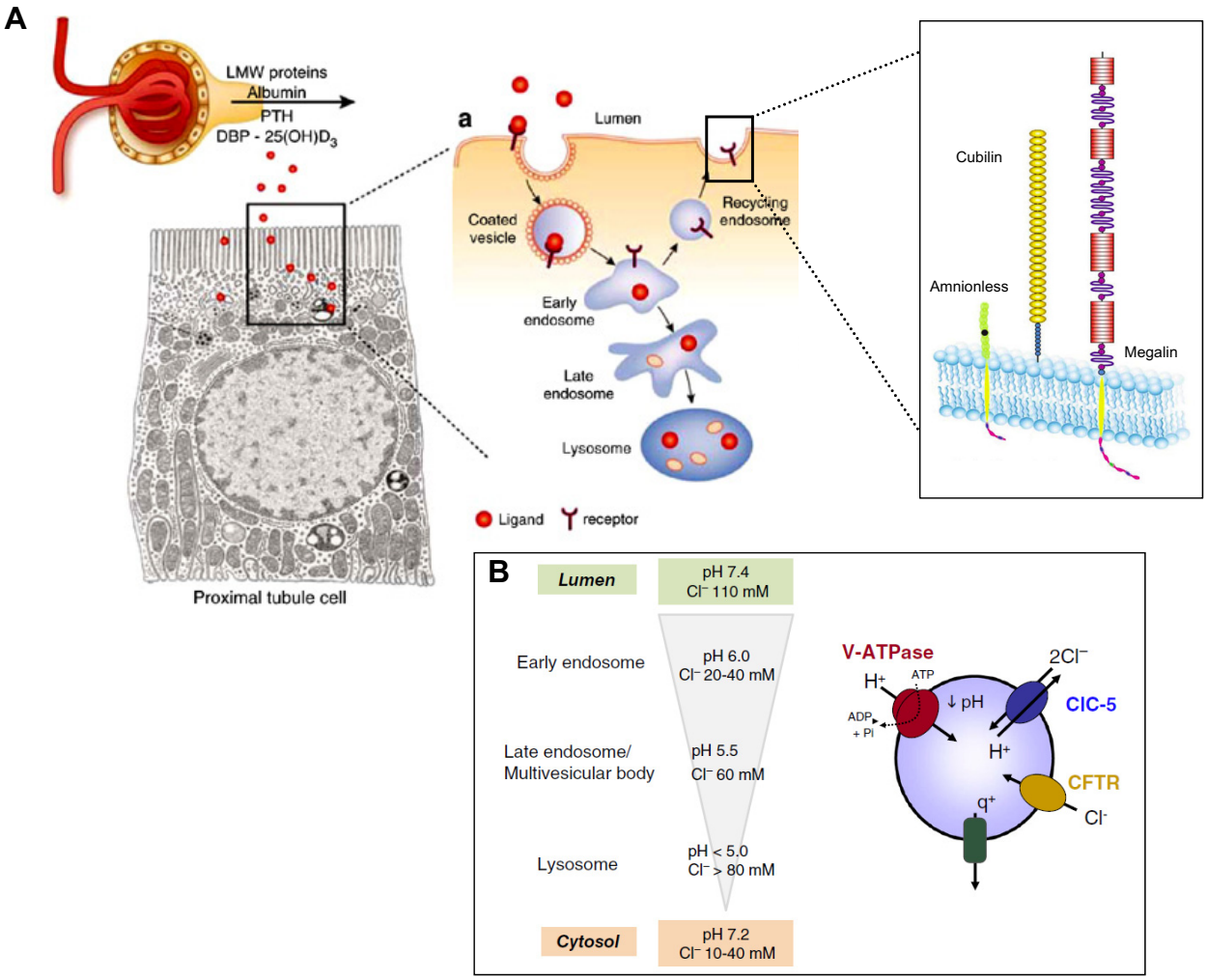


FIGURE 3. Receptor-mediated endocytosis in the proximal tubule of the kidney. *A*: albumin and low-molecular-weight (LMW) proteins, in red, are continuously filtered across the glomerular filtration barrier, to be reabsorbed and processed by the epithelial cells lining the proximal tubule (PT). The LMW ligands first interact with the nonselective megalin/cubilin/amnionless receptor complex at the apical membrane. After internalization, the receptor-ligand complexes progress along the clathrin-dependent endocytic pathway. The endosomes undergo a progressive acidification that results in the dissociation of the receptor-ligand complexes, with the receptors (*inset*) being recycled to the apical membrane, whereas the ligand is directed to acidic lysosomes for degradation. Other possible pathways for albumin handling by proximal tubule cells, including fluid-phase endocytosis and transcytosis back into the circulation, are not detailed. *B*: vesicular acidification and chloride concentration along the endolysosomal pathway. The endocytic pathway in PT cells involves coated pits and coated vesicles, followed by early endosomes that form recycling endosomes or mature to late endosomes and lysosomes. The luminal pH drops from 7.4 in the tubule lumen to 6.0 in early endosomes, 5.5 in late endosomes, and below 5.0 in lysosomes. Such vesicular acidification is necessary for dissociation of the ligand-receptor complex, recycling of receptors to the apical membrane, and progression of ligands into lysosomes. In parallel, the Cl^- concentrations drop from 110 mM in the extracellular space to 20–40 mM in early endosomes, 60 mM in late endosomes, and >80 mM in lysosomes, i.e., much higher than the 10–40 mM in the cytosol. *Right panel*: endosomal acidification that is achieved by ATP-driven transport of cytosolic H^+ through V-ATPase, also known as the proton pump. ClC-5 operates as a Cl^-/H^+ exchanger that facilitates acidification (countercurrent through the $2Cl^-/1H^+$ stoichiometry). The Cl^- channel CFTR is also enriched in the endosomal fraction containing ClC-5, and it participates, together with cation leakage ($q+$), in the electrical shunt necessary for sustained vesicular acidification. CFTR, cystic fibrosis transmembrane conductance regulator; ClC-5, chloride channel 5; V-ATPase, vacuolar H^+-ATPase; q^+, cation. [Adapted from Devuyst and Luciani (160), with permission from John Wiley and Sons; and Jentsch (349).]

in the successive endocytic compartments induces receptor-ligand dissociation and modulates vesicle trafficking, endosomal fusion events, and coat formation (328). In PT cells, endosomal acidification is driven by the electrogenic vacuolar H^+-ATPase (V-ATPase) **(FIGURE 3)**. The translocation of protons from the cytoplasm into the endosomes generates a transmembrane electrical potential ($\Delta\Psi$) with rapid inhibition of V-ATPase activity. The

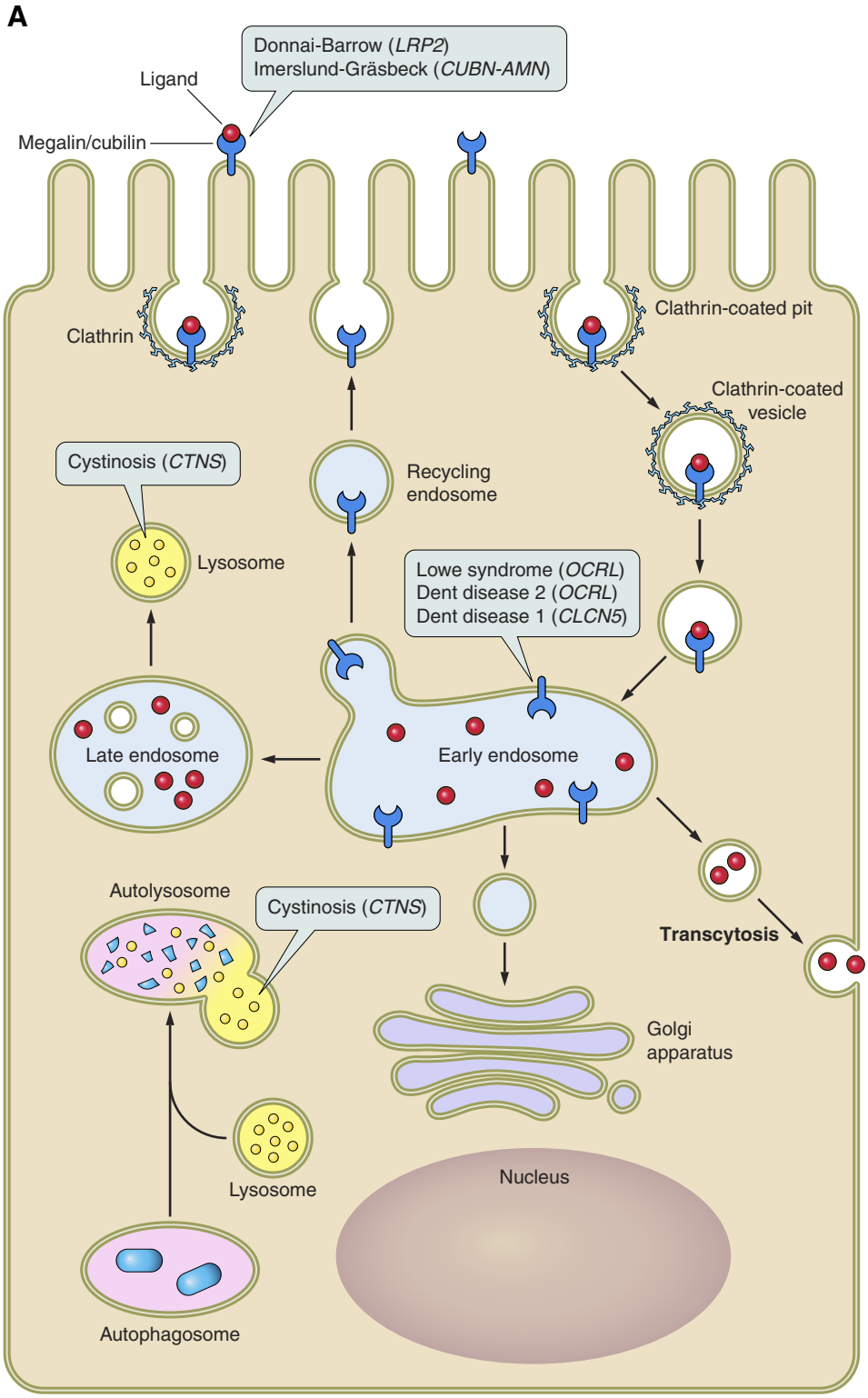


FIGURE 4. Rare disorders targeting the endolysosomal system in the proximal tubule, resulting in renal Fanconi syndrome. *A*: the main endocytic receptor for the clearance of filtered proteins is megalin (encoded by the *LRP2* gene), a member of the low-density lipoprotein receptor gene family. Cubilin (encoded by the *CUBN* gene) is another apical cell surface receptor in proximal tubule (PT) cells, associated with megalin and the amnionless subunit (not represented, encoded by *AMN*) to form a receptor complex for the trafficking of cargo through the early endosomes, late endosomes, and lysosomes of the cell. Endocytic activity in these cells critically requires the actions of *CLCN5* and *OCRL*. *CLCN5* encodes ClC-5, a Cl^-/H^+ exchanger that facilitates acidification and trafficking of endosomal vesicles. *OCRL* encodes inositol polyphosphate-5-phosphatase, which is required for proper vesicular trafficking between intracellular compartments and the plasma membrane. The lysosomal activity, important for cargo processing and autophagy, requires a functional cystinosin, a H^+-cystine cotransporter encoded by the *CTNS* gene. Several disorders are caused by mutations of genes coding for components of the endo-lysosomal system in the PT, including *LRP2* (Donnai-Barrow syndrome), *CUBN* and *AMN* (Imerslund-Gräsbeck syndrome), *CLCN5* (Dent disease 1), *OCRL* (Lowe syndrome and Dent disease type 2), and *CTNS* (nephropathic cystinosis). Typically, these disorders cause PT dysfunction and lead to inappropriate urinary loss of solutes and, often, to renal failure. *B*: phenotype of PT dysfunction in the ClC-5 knockout (KO) ($Clcn5^{Y/-}$) mouse model of Dent disease 1. *i*) Compared with wild-type ($Clcn5^{Y/+}$) littermates, $Clcn5^{Y/-}$ mice show polyuria, with inappropriate glucosuria, calciuria, phosphaturia, and proteinuria. *ii*) Immunoblot analysis confirms the urinary loss of low-molecular-weight proteins in $Clcn5^{Y/-}$ mice, including Clara cell protein of 16 kDa (CC16), transferrin, vitamin D-binding protein (DBP), and cathepsin B. *iii*) The molecular basis of the defective endocytosis is the loss of apical receptors megalin and cubilin in PT cells, as shown by decreased apical signal on immunofluorescence; and *iv*) by the redistribution of cubilin from the brush border to intracellular compartments in subcellular fractions (Percoll gradient) of the kidneys. [Modified from De Matteis et al. (148) and Willnow (813).]

maintenance of V-ATPase activity depends on the dissipation of $\Delta\Psi$, either by cation leakage or by chloride transport (571). Vesicular acidification requires in most cases a chloride (Cl^-) conductance. The intravesicular Cl^- concentration progressively increases from early endosomes (20–40 mM) to lysosomes (>80 mM) (705). It can directly affect the V-ATPase activity (497) as well as other ionic movements and vesicle recycling independently of its effect on pH (199, 705).

Impairment of PT transport processes leads to the loss of LMW proteins and solutes (e.g., phosphate, glucose, amino acids, urate) in the urine. The clinical entity of generalized PT dysfunction is referred to as renal Fanconi syndrome (or

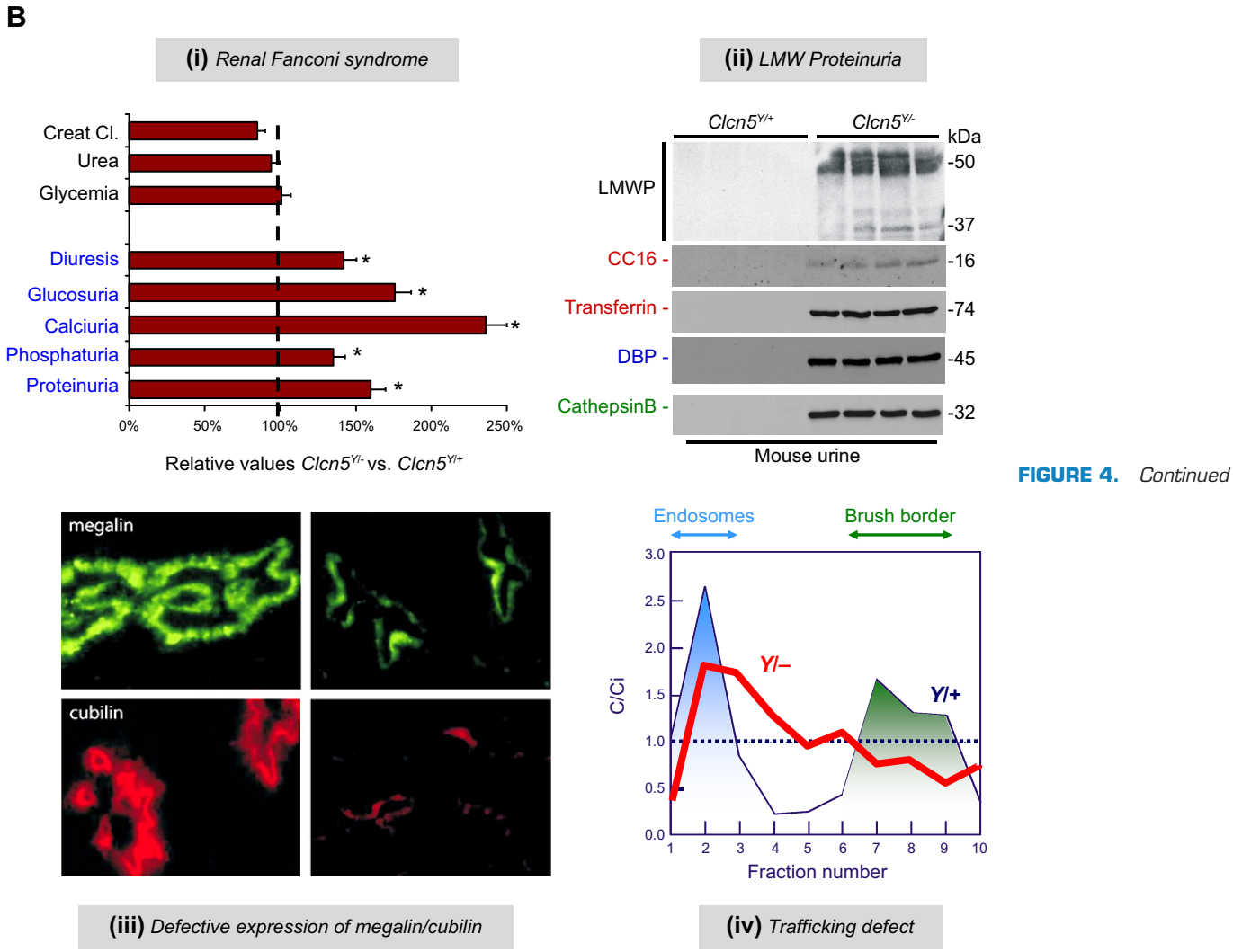


FIGURE 4. *Continued*

de Toni-Debré-Fanconi syndrome) to acknowledge the first description of such a case by Guido Fanconi at the Kinderspital Zurich in 1931 (197). The renal Fanconi syndrome (RFS) is characterized by the urinary loss of the above solutes and LMW proteins, causing dehydration and electrolyte imbalance, rickets, muscular weakness, growth retardation, and progressive renal failure (77, 389). The syndrome can be isolated or associated with multi-systemic disorders; it is variable in terms of severity, duration, extent of tubular dysfunction, and progression towards CKD. These variable clinical presentations reflect at least in part the causal disorder. The RFS can be acquired, for instance induced by exogenous susbstances (toxins, drugs) or associated with autoimmune disorders, or result from inherited disorders **(TABLE 2)** including endolysosomal diseases (e.g., Dent disease, cystinosis), metabolic disorders (e.g., Fanconi-Bickel syndrome, Wilson disease, tyrosinemia, galactosemia, congenital fructose intolerance) (165, 389, 695), or various types of mitochondrial dysfunctions (189, 596). Besides generalized PT dysfunction, isolated defects of proximal transport systems, such as disorders of glucose, urate, or phosphate transport, may also occur and will be discussed separately. In this section we discuss Dent disease and cystinosis **(FIGURE 4)**, two inherited disorders of the endolysosomal pathway that are invariably associated with variable forms of PT dysfunction (57, 515).

2. Dent disease

A) BRIEF CLINICAL DESCRIPTION. Dent disease (also named *X*-linked hypercalciuric nephrolithiasis, *X*-linked recessive hypophosphatemic rickets, *X*-linked recessive nephrolithiasis, or idiopathic LMW proteinuria) is a rare *X*-linked renal tubulopathy that was first reported by Dent and Friedman in two unrelated English boys with rickets associated with renal tubular damage characterized by hypercalciuria, hyperphosphaturia, LMW proteinuria, and aminoaciduria (156). Dent disease is characterized by LMW proteinuria associated with hypercalciuria, which may lead to nephrolithiasis, nephrocalcinosis, and renal failure. The disease may also be associated with PT dysfunction as evidenced by aminoaciduria, phosphaturia, glycosuria, uricosuria, kaliuresis, and impaired urinary acidification and is frequently complicated by rickets or osteomalacia. Usually these fea-

Table 2. *Causes of proximal tubule dysfunction (renal Fanconi syndrome)*

Idiopathic
Autosomal recessive or dominant
X-linked
Hereditary*
Arthrogryposis, renal dysfunction and cholestasis 1; ARCS1 (*VPS33B*)
Arthrogryposis, renal dysfunction and cholestasis 2; ARCS2 (*VIPAS39*)
Cystinosis (*CTNS*)
Cystinuria (*SLC3A1*, *SLC7A9*)
Dent disease 1 (*CLCN5*)
Dent disease 2 (*OCRL*)
Donnai–Barrow syndrome (*LRP2*)
Fabry disease (*GLA*)
Fanconi renotubular syndrome 1; FRTS1 (-)
Fanconi renotubular syndrome 2; FRTS2 (*SLC34A1*)
Fanconi renotubular syndrome 3; FRTS3 (*EHHADH*)
Fanconi renotubular syndrome 4; FRTS4 (*HNF4A*)
Fanconi–Bickel syndrome (*SLC2A2*)
Galactosemia (*GALT*)
Glycogen storage disease type I (von Gierke disease) (*G6PC*)
Hereditary fructose intolerance (*ALDOB*)
Imerslund–Gräsbeck syndrome (megaloblastic anemia 1; *CUBN, AMN*)
Iminoglycinuria (*SLC6A20, SLC6A19, SLC36A2*)
Lowe oculocerebrorenal syndrome (*OCRL*)
Maturity-onset diabetes of the young type 3 (*HNF1A*)
Renal tubular acidosis proximal, autosomal recessive (*SLC4A4*)
Tyrosinemia type I (*FAH*)
Wilson disease (*ATP7B*)
Renal Fanconi syndrome, autosomal dominant, with kidney failure (*GATM*)
Mitochondriopathies
Acquired
Myeloma
Sjögren syndrome
Renal transplantation
Acute tubulointersitial nephritis with uveitis (TINU) syndrome
Autoimmune interstitial nephritis and membranous nephropathy
Primary biliary cirrhosis
Renal hemosiderosis
Exogenous substances
Drugs: aminoglycosides, salicylate, valproic acid, Chinese herbs, ifosfamide, cisplatin, imatinib, mesylate, adefovir, cidofovir, tenofovir, zoledronic acid, deferasirox
Chemical compounds: paraquat, bismus, methyl-3-chromone, 6-mercaptopurine, toluene
Heavy metals: lead, cadmium, mercury, chromium, platinum
Honeybee stings: melittin

*Causative genes are in italics.

tures are present in males only, who may develop bone pain, rickets, failure to thrive, or even renal stones from early childhood. LMW proteinuria is the most consistent manifestation of Dent disease and is identified in almost all affected males and obligate female carriers (57, 165). Of note, proteinuria worsens with age and may reach the nephrotic range (>2 g/day), with evidence of glomerular lesions on renal biopsy (57, 220).

Generalized PT dysfunction (complete RFS) is rare in Dent disease (~10% of patients), whereas the presence of partial RFS (including LMW proteinuria and hypercalciuria with at least one manifestation of PT dysfunction) is detected in 70% of patients (57). Vitamin A deficiency and impaired night vision may be present and are due to the urinary loss of retinol binding protein (37). Hypercalciuria and nephrocalcinosis are also highly prevalent, although there is inter- and intrafamilial variability in the occurrence of nephrolithiasis which occurs in approximately half of the affected males (57, 164). Pseudo-Bartter syndrome, with renal losses of salt and K^+ and secondrary hyperaldosteronism, has been reported, increasing in frequency with age (57). A cumulative analysis of the clinical data from 377 male patients confirmed the main manifestations of the disease, and the occurence of micro- or macrohematuria, proteinuria in the nephrotic range, urinary concentration defect, Bartter-like phenotype, hypomagnesemia, and defects in urinary acidification (458).

Progression to end-stage renal failure occurs between the third and the fifth decades of life in 30–80% of affected males (57, 653). The link between nephrocalcinosis and renal failure has not been established in patients. The occurrence of these predominantly renal manifestations and their association with mutations in the *CLCN5* gene is referred to as Dent disease 1. A minority of patients with Dent disease present extra-renal manifestations such as mental developmental delay, hypotonia, and cataract, in association with mutations of the oculo-cerebrorenal syndrome of Lowe (*OCRL*) gene (306). The occurrence of these extra-renal manifestations associated with *OCRL* mutations is referred to as Dent disease 2.

B) GENETICS. Dent disease 1 (MIM no. 300009) is caused by inactivating mutations in the *CLCN5* gene (Xp11.22), which encodes the 746-amino acid electrogenic $2Cl^-/H^+$ exchanger ClC-5 (439, 567, 652). ClC-5 is a member of the CLC family of Cl^- channels/transporters and belongs to a cluster of three isoforms (ClC-3, ClC-4, ClC-5) that are mainly located in intracellular vesicles. ClC-5 is characterized by 18 α-helices, with two phosphorylation sites and one *N*-glycosylation site. Crystal structures of bacterial and eukaryotic CLCs showed that the protein forms diamond-shaped homodimers composed of two repeated halves that span the membrane in opposite orientations. Each subunit

has its own pore responsible for the selective coupling of the Cl^- flux to H^+ countertransport (183, 201, 349).

The described *CLCN5* mutations include large deletions (4%) as well as nonsense (17%) and frameshift (28%) mutations that produce premature stop codons, splice-site mutations (11%) predicted to interfere with correct splicing, and missense (37%) and small in-frame deletions (2.6%) affecting conserved residues (458). The mutations are scattered through the coding region, with no evidence for mutational hot spots (458, 823). Most of the *CLCN5* mutations (missense and nonsense) are predicted to result in a truncated or absent ClC-5 protein, which would lead to a complete loss of its antiporter function. Heterologous expression in *Xenopus laevis* oocytes or HEK293 cells has shown that most *CLCN5* mutations lead to a loss of Cl^- conductance (439). Further detailed studies of the *CLCN5* missense mutations revealed that these may lead to impaired processing and folding, with endoplasmic reticulum (ER) retention and degradation by quality control mechanisms (class 1); delay in processing and reduced stability (class 2); and normal trafficking but altered electrical activity (class 3) (446). Some mutations of *CLCN5* cluster at the dimer interface, which could impair dimerization and lead to rapid degradation of the mutant protein within the cell (446, 458, 824). Examination of a large cohort of 109 male patients with *CLCN5* mutations (Dent disease 1) could not establish a correlation between severe and moderate mutations (classified according to the types of mutations) and the phenotype at diagnosis, the decrease in eGFR, and tubular manifestations (57). A considerable intra-familial variability in disease severity has been reported, including for the extent of PT dysfunction and urinary wasting of bicarbonate and ions associated with a given *CLCN5* mutation (458).

There is genetic heterogeneity for Dent disease, with ~50–60% of patients harboring *CLCN5* mutations, ~15% with *OCRL* mutations, and the remaining 25–35% of patients having neither *CLCN5* nor *OCRL* mutations. Dent disease 2 (MIM no. 300555) defines patients with Dent disease who have extrarenal manifestations and share mutations in the *OCRL* gene with the oculo-cerebrorenal syndrome of Lowe (306, 688). There is a wide overlap between the manifestations of PT dysfunction in patients with Dent disease type 1 (*CLCN5* mutations) and Dent disease 2 (*OCRL* mutations), with all patients manifesting LMW proteinuria and ~90% hypercalciuria (76). The mild extrarenal manifestations of patients with Dent disease 2 include elevated levels of creatine phosphokinase (CPK) and/or lactate dehydrogenase (LDH), indicating muscle involvement, mild intellectual disability, mild developmental delay, and cataract; these manifestations are much less severe than in Lowe syndrome. Similarly, patients with Dent disease 2 are less likely to have nephrocalcinosis and urinary wasting of phosphate, amino acids, bicarbonate, and K^+, and a slower decrease in eGFR compared with patients with Lowe syndrome (76, 148, 848).

The *OCRL* gene encodes the inositol polyphosphate 5-phosphatase OCRL, which preferentially hydrolyzes the 5-phosphate of phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$]. Disease-causing mutations in *OCRL* result in the loss of 5-phosphatase activity and accumulation of $PI(4,5)P_2$ in PT cells of patients with Lowe syndrome (852). The vast majority of *OCRL* mutations associated with Lowe syndrome are located in exons 8–23, which comprises the inositol polyphosphate 5-phosphatase and the ASPM, SPD-2, Hydin (ASH), and RhoGAP-like domains, whereas the majority of mutations that cause Dent disease 2 are located in exons 1–7, which encompass the pleckstrin homology (PH) domain (148). Of note, mutations in the phosphatase domain of *OCRL* have been described both in patients with Lowe syndrome and in patients with Dent disease 2, but such mutations in patients with Dent disease 2 are always missense mutations (298). A number of evidences suggest that OCRL plays a role in the endocytic pathway and the coordination of membrane dynamics with remodeling of the actin cytoskeleton (148, 193, 475). Therefore, it is likely that *OCRL* mutations in Lowe syndrome or Dent disease 2 lead to disruptions in the endosomal and/or lysosomal trafficking, i.e., an abnormality similar to that observed in Dent disease 1.

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. The clinical presentation Dent disease 1 reflects the predominant expression of ClC-5 in PT cells, where it codistributes with the V-ATPase in subapical, early endosomes (158, 271). Studies in two independent strains of *Clcn5* knockout (KO) mice have provided important insights into the mechanisms of PT dysfunction in Dent disease 1 (570, 794). The *Clcn5* KO mouse models recapitulate the LMW proteinuria and other manifestations of PT dysfunction associated with the disease **(FIGURE 4)**. In vitro experiments showed defective acidification of vesicles isolated from *Clcn5* KO mice, supporting a role for ClC-5 in acidification of early endosomes (272, 529). Although ClC-5 was initially considered as a simple Cl^- channel, later studies revealed that it is actually an electrogenic $2Cl^-/H^+$ exchanger, exploiting the H^+ gradient to move Cl^- into endosomes (567, 652) **(FIGURE 3)**. To better understand the biological role of this exchange activity and its relevance for Dent disease, Novarino et al. (529) generated a knock-in (KI) mouse model carrying a point mutation (E211A) affecting a glutamate residue that is crucial for the gating of CLC exchangers. The replacement of this glutamate by an alanine converts ClC-5 into a pure, uncoupled Cl^- conductor. The E211A mutant ClC-5 did not affect endosomal acidification, in contrast with the severe defect observed in ClC-5 KO. However, despite the normal endosomal acidification, the KI mice showed the same phenotype as that of *Clcn5* KO mice, including LMW proteinuria, glycosuria, hyperphospha-

turia, and hypercalciuria. Furthermore, a similar uncoupling mutation (E211Q) has been reported in a Japanese patient with Dent disease (672) supporting that PT dysfunction in Dent disease may thus occur despite normal endosomal acidification. Instead of the simple Cl^- shunt hypothesis, the disease may be caused by defective exchange activity, i.e., uncoupling of Cl^- from H^+ gradients and defective endosomal Cl^- accumulation. ClC-5 could actually mediate endosomal acidification independently of the V-ATPase in the early endosomes, with luminal H^+ uptake driven by the favorable gradient for Cl^- (652) **(FIGURE 3)**. Recent studies in conditionally immortalized PT cells from patients with mutations involving different domains of ClC-5 showed differing effects on endosomal acidification, uncoupled to defects in receptor-mediated endocytosis (257). A potential role of vesicular Cl^- concentration or transmembrane voltage of endosomes, which could affect other transport systems or vesicule recycling, has been hypothesized (350, 705).

Studies in *Clcn5* KO and KI mice have demonstrated that inactivation of ClC-5 is associated with a severe trafficking defect in PT cells **(FIGURE 4)**, with loss or reduced levels of megalin and cubilin at the brush border, impaired endocytosis and lysosomal processing of endocytosed ligands, and defective internalization of NaP_i-IIa and/or Na^+/H^+ exchanger 3 (NHE3) (121, 529, 570, 794). Importantly, mice lacking ClC-5 do not show ultrastructural alterations of the endocytic apparatus (121), a finding confirmed in kidney biopsies from patients with Dent disease and established mutations in *CLCN5* (501). The use of differentiated primary PT cells grown on filters evidenced that the endocytic defect observed in *Clcn5* KO mice was retained in vitro (225, 594, 738). The link between ClC-5 expression, receptor-mediated endocytosis, and PT dysfunction was further supported by a proof-of-concept study investigating the effect of bone marrow transplantation in *Clcn5* KO mice (225). Transplantation of wild-type bone marrow in *Clcn5* KO mice significantly improved PT dysfunction, with bone marrow-derived cells engrafted in the kidney, surrounding PT cells which showed a rescue of the apical expression of ClC-5 and megalin receptors. The improvement of PT dysfunction correlated with the rescue of *Clcn5* gene expression in kidneys. Coculture of *Clcn5* KO mouse PT cells (mPTCs) with bone marrow-derived cells confirmed rescue of ClC-5 and megalin, resulting in improved endocytosis. Nanotubular extensions between the engrafted bone marrow-derived cells and PT cells were observed in vivo and in vitro, playing a key role in the rescue mechanism (225).

Despite their vulnerability, PT cells are able to recover from an ischemic or toxic insult, as surviving cells dedifferentiate and proliferate to eventually restore tubular integrity (66). A similar process occurs in Dent disease, with a fourfold increase in the proliferative activity of PT cells [assessed by transcription of proliferating cell nuclear antigen (PCNA), KI-67, and cyclin E] paralleled by dedifferentiation (expression of osteopontin and the mesodermal marker carbonic anhydrase type III, CA3). The induction of the latter was also linked to an increased production of superoxide anion and the induction of type I superoxide dismutase and thioredoxin, pointing to increased oxidative stress and solicitation of cell oxidative defenses in *Clcn5* KO kidneys (229). Of note, these modifications occurred at a time when no visible alterations in cell morphology or renal failure were observed in *Clcn5* KO mice, and neither was there any change in the apoptotic rate. Albumin is also known to exert a potent survival activity in mouse PT cells, most likely through scavenging of reactive oxygen species (335), so that a reduced capacity of albumin uptake may be deleterious.

The potential link between the functional loss of ClC-5 and PT dysfunction can be proposed as follows. The defective Cl^- transport in early endosomes leads to impaired trafficking and recycling of apical receptors, defective receptor-mediated endocytosis, and ensuing urinary loss of LMW ligands (121). The functional loss of ClC-5 is also associated with impaired lysosomal function, as shown by the defective processing of endocytosed LMW ligands (121). The lysosome defect may at least in part be due to defective megalin which is critical for reabsorbing (mannose 6-phosphate devoid) lysosomal enzymes that are continuously filtered from the circulation, providing a major source of lysosomal enzymes in PT cells (521). In turn, the lysosomal defect might compromise autophagy, the cytoprotective mechanism for the degradation of damaged organelles through lysosome-mediated self-digestion (674). The defective lysosomal-mediated clearance of autophagosomes, containing ubiquitinated proteins and dysfunctional mitochondria, may lead to oxidative stress as observed in ClC-5 KO kidneys (229). It was recently shown that oxidative stress disrupts the integrity of the junctional complex [i.e., zonula occludens 1 (ZO-1) protein] (845), which might activate an abnormal signaling cascade involving the ZO-1-associated nucleic acid binding protein (ZONAB, also called Y-box protein 3, YBX3), a transcription factor known to cause proliferation (increased transcription of cyclin D1 and PCNA) and apical dedifferentiation (repression of the transcription of megalin and cubilin) in proximal tubule cells (433). The crucial pathogenic role of oxidative stress in mediating the epithelial dysfunction associated with endolysosomal diseases will be elaborated in the section dealing with nephropathic cystinosis (207, 591). Of note, the fact that ClC-5 is also detected in cells lining the thick ascending limb of Henle's loop and in the α-type intercalated cells of the collecting ducts (CD) (158) may explain some of the distal tubular manifestations of the disease, including defects in urinary acidification (458).

Inactivating mutations in the inositol polyphosphate 5-phosphatase OCRL induce defects in the endolysosomal system

which generally mimicks the PT dysfunction encountered in Dent disease 1. The similar phenotype is explained by the association of OCRL with early endosomes, where it acts to maintain low levels of $PI(4,5)P_2$ for proper endocytic trafficking (754, 774). The functional loss of OCRL induces an increase in $PI(4,5)P_2$ levels in early endosomes, which stimulates uncontrolled actin polymerization and impairs the trafficking of different receptors including megalin (774). These events lead to the trapping of megalin in early endosomes, reducing its recycling to the plasma membrane, impairing receptor-mediated endocytosis and causing PT dysfunction (148). The absence of OCRL is also leading to $PI(4,5)P_2$ accumulation on autolysosomal membranes, causing defective autophagic flux and increased levels of autophagosomes, which could be toxic for PT cells (146).

If the link between deficient ClC-5 or OCRL and defective PT apical endocytosis has been established, the transition between such PT dysfunction and progression to CKD in Dent disease remains to be deciphered. Atypical features (nephrocalcinosis, fibrosis) are observed in the few kidney biopsies available (858). The classical mechanisms of albumin toxicity on PT cells, which are considered in case of glomerular proteinuria, cannot be evoked here, since PT cells in Dent disease are prevented from endocytosis-mediated albumin overload. Presumably, early changes in PT cells, including proliferation, dedifferentiation, autophagy, and metabolic adaptation, may become maladaptive and promote inflammation and progression of tubulointerstitial fibrosis by various mechanisms (241, 436). The role of tubular proteinuria, a universal feature of the disease, should also be considered, as increasing evidence suggests that distal nephron segments may elicit specific stress response when exposed to proteinuria (178, 185a).

3. Cystinosis

A) BRIEF CLINICAL DESCRIPTION. Cystinosis is a rare disease (incidence: 1:100,000–1:200,000 live births) that is caused by recessive mutations in the *CTNS* gene that encodes the lysosomal cystine-H^+ cotransporter cystinosin (111, 364, 748). *CTNS* is expressed in all tissues: mutations causing cystinosis result in a lysosomal storage disorder characterized by a multi-systemic accumulation of cystine crystals. Children with infantile cystinosis (MIM no. 219800), the most frequent and most severe form of cystinosis, develop RFS typically around age 6 to 12 mo, with accompanying polyuria, polydipsia, failure to thrive, and rickets. The GFR begins to deteriorate from 5 to 6 yr of age, leading to ERSD by ~10 yr of age if untreated (188, 227). In addition to the kidney manifestations, patients present early depositions of cystine crystals in the cornea, and can develop retinopathy, hypothyroidism, hypogonadism, diabetes, myopathy, and deterioration of the central nervous system (227, 515). The juvenile (MIM no. 219900) and the ocular (MIM no. 219750) forms of cystinosis are milder and rarer than the typical, infantile cystinosis (227). There is a specific treatment for cystinosis: cysteamine, an aminothiol that can deplete the intralysosomal cystine through the reduction of cystine, and the formation of cysteine and a cysteamine-cysteine mixed disulfide which exits the lysosome via the cationic amino acid transporter PQLC2 (352, 435). Most of these complications, with the exception of the RFS, can be delayed or attenuated with cysteamine therapy (81, 414).

B) GENETICS. More than 100 pathogenic mutations of the *CTNS* gene (17p13.2) have been reported (188). Founder mutations, including a 57-kb deletion in *CTNS* which affects 65% of patients of northern European descent but is almost completely absent in patients from other origins, have been described (110). Genotype-phenotype correlation revealed that severe or truncating mutations on both alleles are usually associated with infantile cystinosis, while juvenile and ocular forms of cystinosis are usually associated with at least one mild mutation. However, some missense mutations in *CTNS*, which result in mutated forms of cystinosin located in lysosomes but unable to carry cystine transport, have been found in patients with juvenile cystinosis, suggesting that cystinosin exerts functions beyond cystine transport (365).

Cystinosin is a 367-amino acid protein, with seven predicted transmembrane domains, a luminal NH_2-terminal region bearing seven *N*-glycosylation sites and a cystolic COOH-terminal GYDQL lysosomal targeting signal (748). An additional lysosomal targeting motif, YFPQA, reinforces association with lysosomes (111). A longer CTNS isoform (cystinosin-LKG) can be generated by alternate splicing of exon 12, localized into lysosomes, the secretory apparatus, and the plasma membrane (734). Cystinosin is a high-affinity cystine-proton symporter that uses the proton gradient to export cystine from the acidic lysosome to the cytosol **(FIGURE 4)**. Since the low abundance of cystinosin transporters in lysosomes is the rate-limiting step for cystine transport, the disruption of cystine transport results in intralysosomal accumulation of cystine, reflecting the lysosomal degradation of disulfide-bearing proteins, such as albumin which is internalized via receptor-mediated endocytosis. In turn, cystine may organize into crystals within the lysosomal matrix: although these crystals are specific for cystinosis, they are probably not instrumental for the development of PT dysfunction. They are indeed not detected despite early manifestations of PT cell dysfunction in patients and mouse models of cystinosis (110). This conclusion is supported by the lack of effect of cysteamine, which decreases cystine levels, on the manifestations of RFS (81). Instead, multiple alterations in cystinosis cells are probably involved in the functional defects that characterize the early stage of cystinosis. These defects include impaired lysosomal dynamics, with lysosomes engorged by undigested proteins and clustered around the nuclei; defective clearance of endocytic cargo, with also a decreased expression of apical receptors; impaired proteolysis and limited amino acid and cysteine availability in the cytosol, causing redox imbalance and oxi-

dative stress; abnormal clearance of autophagic vesicles and accumulation of damaged mitochondria, which further increases ROS production (see below). In the long term, these modifications may also activate the inflammasome and apoptosis, leading to cell atrophy and irreversible tissue damage (110).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. Studies based on a *Ctns* KO mouse model that recapitulates multiple features of cystinosis have demonstrated that the functional loss of cystinosin is reflected by enlarged, perinuclear lysosomes, abnormal proliferation and dysfunction of PT cells, which showed a progressive loss of the apical expression of megalin and of the glucose (SGLT2) and phosphate (NaP_i-IIa) cotransporters (228, 591). Despite the identification of cellular defects associated with cystinosis in different models and cell systems (see above), a unifying mechanism linking loss of cystinosin, lysosomal dysfunction, and defective transport by PT cells had not been deciphered until recently.

An essential role of the endolysosomal system is to capture and degrade intracellular worn-out constituents through autophagy, particularly in PT cells, whose intense reabsorptive and transport properties require the maintenance of mitochondrial network (215). The autophagy-mediated turnover of damaged mitochondria is required for protecting PT from acute tubular injury (340). Accumulation of distorted mitochondria and of autophagy receptor SQSTM1/p62 in kidney biopsies and urinary cells from cystinotic patients (640) suggested that autophagy could play a role in the PT dysfunction due to cystinosis. Recent studies confirmed that the genetic deletion of cystinosin impaired the autophagy-mediated clearance in vitro and in vivo, due to defective lysosomal degradation capacity (207). In turn, the defective autophagy clearance led to the accumulation of damaged and dysfunctional mitochondria in *Ctns* KO cells, overproducing mitochondrial-derived ROS. A signaling cascade bridging excessive mitochondrial ROS and epithelial dysfunction was deciphered, involving the tight junctions. In differentiated epithelial cells, tight junctions repress the nuclear translocation of ZONAB/YBX3, a transcriptional factor that promotes cell proliferation and represses PT differentiation during kidney development (433). The increased levels of mitochondrial ROS enhanced GNA12/Gα_{12}-SRC-mediated phosphorylation of the tight junction protein ZO-1 and its subsequent misrouting to enlarged, nondegradative endolysosomes. In turn, the disruption of tight junction integrity promotes ZONAB/YBX3 signaling, with increased proliferation (e.g., *Ccnd1*, *Pcna*) and decreased differentiation (e.g., *Lrp2*) targets, resulting in defective endocytosis in *Ctns* KO cells. The biological relevance of the YBX3 signaling for maintaining PT cell integrity was confirmed by gain- and loss-of-function approaches and pharmacological interventions. In particular, treatment of *Ctns* KO mice and their derived PT cells with the mitochondrial-targeted antioxidant MitoTempo, which is clinically tested in various mitochondrial diseases, not only repairs dysfunctional mitochondria and averts mitochondrial oxidative stress, but also rescues the integrity of tight junctions, cell differentiation, and endocytic uptake (207). The identification of this signaling cascade **(FIGURE 5)** substantiates the role of lysosomes in preserving the autophagy-mediated quality control of mitochondria that are crucial for the high transport activities performed by specialized epithelial cells.

4. Other genetic disorders associated with defective receptor-mediated endocytosis

Recent studies have extended the role of receptor-mediated endocytosis in association with other genetic disorders that mimick the PT dysfunction associated with Dent disease. Inactivation of the chloride channel cystic fibrosis transmembrane conductance regulator (CFTR) causes cystic fibrosis (CF) (MIM no. 219700), the most common autosomal recessive disease in Caucasian individuals (613). CFTR is a 1,480-amino acid protein that belongs to the ATP-binding cassette (ABC) family of integral membrane proteins. It is located mainly in the apical membrane area of secretory epithelia, where it functions as a cAMP-dependent chloride channel and as a conductance regulator via interactions with other ion channels (683). CFTR is significantly expressed in the kidney, located in the apical area of PT cells, where it codistributes with ClC-5 in PT endosomes **(FIGURE 3)** (357). Defective receptor-mediated endocytosis has been demonstrated in CFTR-null mice, with impaired LMW protein (β2-microglobulin) uptake and a waste of cubilin and its LMW ligands into the urine. A significant LMW proteinuria (and particularly transferrinuria) was also documented in the *Cftr*$^{delta/delta}$ mice and in a cohort of patients with CF. Several reasons could explain the milder renal phenotype that is observed in *Cftr* KO mice and patients with CF in comparison with *Clcn5* KO mice and patients with Dent disease. First, the difference could reflect the more distal distribution of CFTR as compared with ClC-5 along the PT. Indeed, although ClC-5 is distributed evenly in the S1 to S3 parts of the PT, CFTR seems to be most abundant in the S3 segment of the PT, which displays lower endocytic activity (357). Second, CFTR functions as a cAMP-regulated, ATP-dependent chloride channel, whereas the flux of chloride through ClC-5 depends constitutively on transmembrane Cl^- and H^+ concentration gradients, together with the membrane voltage. Third, the discrete nature of renal manifestations in CF might be due to tissue-specific protective mechanisms, such as the occurrence of functional CFTR splice variants (493), or alternative pathways for Cl^-.

Hepatocyte nuclear factor 1α (HNF1α) is a homeodomain-containing transcription factor expressed in the liver, pancreas, and proximal tubule of the kidney (749). HNF1α binds to DNA as a homodimer or a heterodimer with the

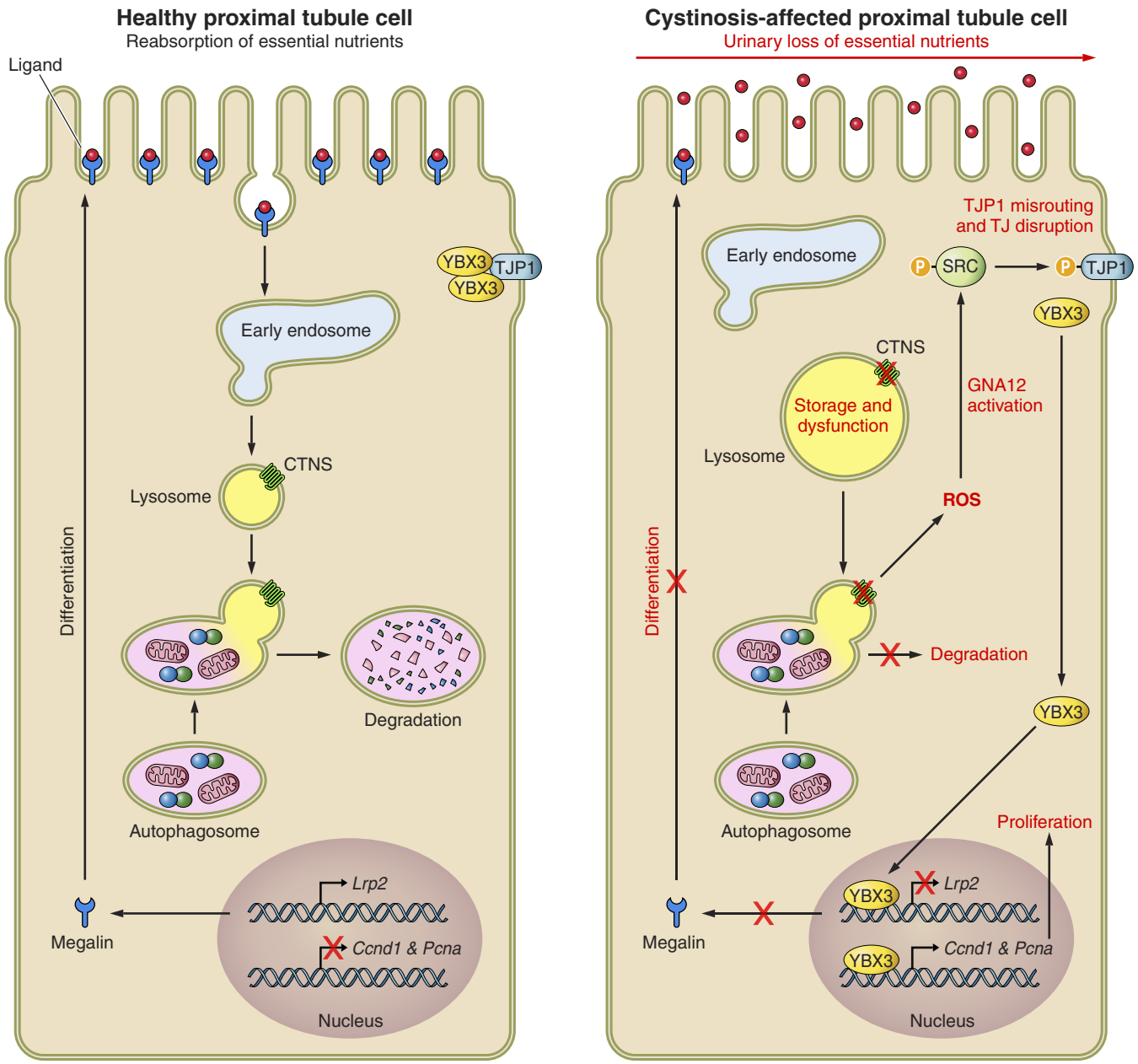


FIGURE 5. Cascade linking primary lysosomal defect and proximal tubule dysfunction in cystinosis. Inactivating mutations in the lysosomal transporter cystinosin (CTNS) cause lysosomal dysfunction storage disease within proximal tubule cells. The ensuing lysosomal dysfunction impairs the cellular degradation of autophagosomes containing SQSTM1$^+$ aggregates and/or damaged mitochondria, promoting the generation of reactive oxygen species (ROS). In turn, the ROS stimulate GNA12-SRC-mediated phosphorylation of the TJP1 adapter protein, resulting in its misrouting to an endolysosomal compartment. The disruption of tight junction integrity releases the transcription factor YBX3, which induces abnormal cell proliferation (induction of the transcription of *Ccnd1* and *Pcna*, coding for proliferation factors) and represses apical endocytic receptors such as megalin (M coded by *Lrp2*), causing epithelial dysfunction in cystinosis cells. TJ, tight junction. [Adapted from Festa et al. (207).]

closely related HNF1β. HNF1α is only found in PT cells, whereas HNF1β is expressed in most nephron segments. Heterozygous mutations of HNF1α cause an autosomal dominant form of diabetes mellitus (MODY-HNF1A) and kidney tubular dysfunction (574). The *Hnf1*α KO mice show LMW proteinuria and decreased uptake of β2-microglobulin, indicating a major endocytic defect due to decreased expression of megalin/cubilin receptors (739). The promoters of the *LRP2* and *CUBN* genes coding for megalin and cubilin, respectively, contain binding sites for HNF1α. The functional interaction of HNF1α with these promoters was demonstrated in vitro. The expression of *Clcn5* was reduced in the proximal tubule segments of HNF1α-null kidneys, and it was rescued, with a parallel

increase in receptor-mediated endocytosis, upon transfection of HNF1α-null cells with wild-type but not with mutant HNF1α. Importantly, LMW proteinuria was consistently detected in individuals with HNF1A mutations compared with healthy controls and patients with non-MODY-HNF1A diabetes mellitus (739). Thus HNF1α plays a key role in the constitutive expression of megalin and cubilin, hence regulating receptor-mediated endocytosis in the kidney.

B. Disorders of Uric Acid Handling

1. Uric acid regulation by the kidney

Uric acid is produced by dietary and endogenous purine metabolism mostly in the liver, where it is generated from xanthine by the xanthine oxidase. In most mammals, uric acid is further metabolized by the hepatic enzyme uricase (encoded by the *Uox* gene) to highly soluble allantoin, which can be readily excreted in the urine. In humans, this uricase is inactive as a result of mutational silencing making uric acid the final breakdown product of purine metabolism (826, 827). Uric acid is a weak diprotic acid which exists predominantly as monosodium urate anion at physiological pH of 7.4. The terms urate and uric acid are often interchangeably used to refer to the total pool of dissociated and undissociated uric acid in the circulation, since the ratio of urate to uric acid remains stable with constant pH. This ratio is much more variable in the urine with broader range of pH. Lower urinary pH values result in a larger proportion of uric acid in the undissociated form (60). Hyperuricemia has been linked to various diseases including gout, hypertension, as well as cardiovascular and renal disease (200, 355, 699). In particular, the issue of whether urate contributes to kidney disease, hypertension, or diabetes remains controversial (354). On the other hand, urate seems to have a protective role as a potent antioxidant, and low serum urate concentrations have been associated with several neurological diseases (548). Serum urate levels depend on both urate production and its removal by the kidney and intestine. Although production of urate through dietary purine intake or alterations in purine metabolism affect serum urate concentrations, changes in serum urate levels are mostly due to impaired renal excretion (333, 669).

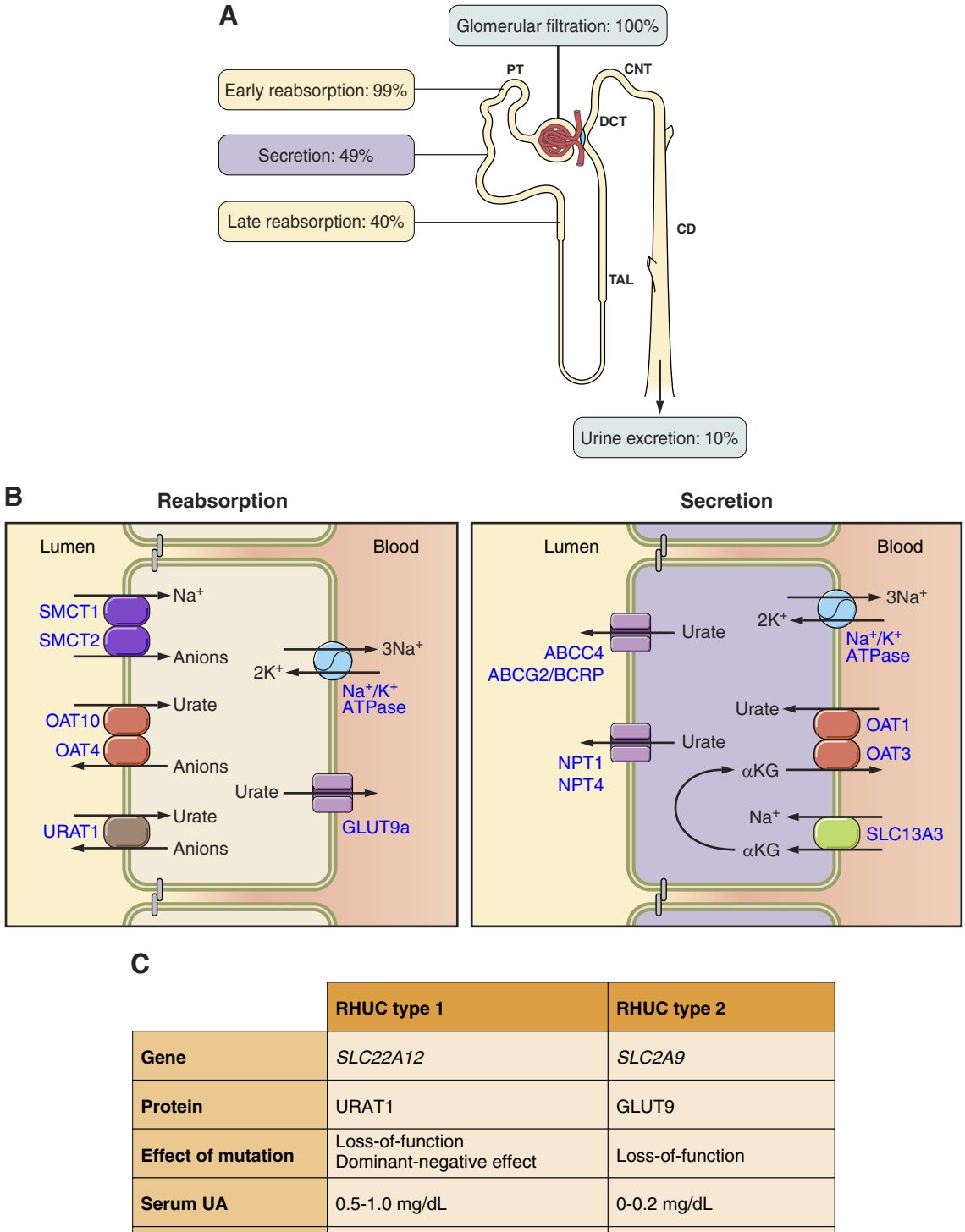
Approximately two-thirds of daily urate production is excreted by the kidney, the remainder being eliminated by the gastrointestinal tract. Previous physiological and pharmacological studies have suggested a bidirectional transport of urate in the PT. A four-component model has been accepted for many years, which proposed that urate handling by the kidney consists of four steps: glomerular filtration, reabsorption of nearly all of the filtered urate in the early PT, subsequent tubular secretion of up to half of this amount, and finally postsecretory reabsorption of the majority of the secreted urate in the late PT with only ~10% of the filtered urate being excreted into the urine **(FIGURE 6)**. This model was based on an interpretation of the pharmacological interactions of antiuricosuric and uricosuric agents (169, 612, 689, 706). Secreted urate was suggested to contribute moderately to urate excretion, implying that the excreted urate represents mainly the filtered urate that escapes reabsorption (60, 502, 503, 589, 617, 618). However, the recent molecular identification of key urate transporters allowed a better understanding of urate handling in the kidney, showing the importance of urate secretion in urate homeostasis.

The exact molecular mechanisms that control urate handling in the kidney are not yet completely understood, although the molecular identification of the kidney-specific urate/anion exchanger URAT1 in 2002 by Enomoto et al. promoted the discovery of several transporters involved in urate transport (17, 191). These transporters include NPT1 (360), ABCC4 (761), SMCT1 (253), SMCT2 (254), OAT10 (29), GLUT9 (16, 99, 778), ABCG2/BCRP (816), as well as urate transport-related scaffolding protein PDZK1 (18). Their identification promoted the idea of a urate-transporting multimolecular complex, the "urate transportome" (17) **(FIGURE 6)**

In plasma, urate mostly exists as an organic anion, which is freely filtered by the glomerulus. In the PT, a complex interplay of various transport pathways is involved in the reabsorption of filtered urate. The PT cells are primed for apical urate transport by the Na^+-dependent absorption of lactate and other monocarboxylate anions, which increases the intracellular concentration of anions that exchange with luminal urate. This process is mediated by the apical Na^+-coupled monocarboxylate cotransporters 1 (SMCT1) and 2 (SMCT2), respectively, encoded by the *SLC5A8* and *SLC5A12* genes, which colocalize with urate transporters at the apical membrane of PT cells (503). Urate-anion exchange in turn involves the urate transporter URAT1, encoded by the *SLC22A12* gene, and the organic anion transporters OAT4 and OAT10, which are encoded respectively by the *SLC22A11* and *SLC22A13* genes (29, 191, 278). Exit of urate from the PT cell is mediated by the basolateral voltage-dependent urate transporter GLUT9a (15, 503, 633, 778). The secretion of urate by the PT is a mirror image of the urate uptake. It involves the basolateral urate transporters OAT1 and OAT3, transporting the anion into the cell in exchange for α-ketoglutarate, followed by secretion via the ATP-driven efflux pumps ABCC4 (ATP-binding cassette C4, encoded by the *ABCC4* gene) and ABCG2/BCRP (ATP-binding cassette subfamily G member 2 or breast cancer resistance protein, encoded by the *ABCG2* gene) and the electrogenic apical urate transporters NPT1 and NPT4 (encoded by the *SLC17A1* and *SLC17A3* genes) (336, 359, 360, 503, 761, 816) **(FIGURE 6)**.

Serum urate levels display a strong genetic predisposition, with a heritability of ~40–70% (405). Various GWAS

pointed to several genetic loci associated with serum urate concentration. These loci include urate transporter-coding genes including *SLC2A9* (GLUT9), *ABCG2* (ABCG2/BCRP), *SLC17A1* (NPT1), *SLC17A3* (NPT4), *SLC22A11* (OAT4), *SLC22A12* (URAT1), and *PDZK1* (PDZK1/NHE-RF3) (17, 106, 151, 179, 395, 405, 430, 542, 744, 778, 837). A very large effect was identified for the *SLC2A9* and *ABCG2* loci, explaining respectively 3 and 1% of the variance in serum urate concentration (405). The important role of GLUT9 (*SLC2A9*) in urate handling will be de-



C

	RHUC type 1	RHUC type 2
Gene	*SLC22A12*	*SLC2A9*
Protein	URAT1	GLUT9
Effect of mutation	Loss-of-function Dominant-negative effect	Loss-of-function
Serum UA	0.5-1.0 mg/dL	0-0.2 mg/dL
FE_{UA}	40-90%	~150%
UA transport defect	Early reabsorption defect	Total reabsorption defect

scribed below (see sect. III*B2*B*II*). ABCG2 was initially identified as a multidrug resistance protein (181). Dehghan et al. (151) were the first to indicate a role for ABCG2 in urate handling through a GWAS showing that the *ABCG2* locus is associated with serum urate level and gout. ABCG2 was subsequently found to be a high-capacity urate transporter. Using a *Xenopus* oocyte expression system, Woodward et al. (816) demonstrated that ABCG2 mediates urate efflux. The role of ABCG2 as a high-capacity urate transporter was verified by Matsuo et al. (469) using membrane vesicles from transfected HEK293 cells. Several loss-of-function *ABCG2* variants that confer a risk of hyperuricemia and gout have been identified, including the common variant Q141K, which reduces urate efflux by 54% (816).

Matsuo et al. (469) investigated the relationship between ABCG2 dysfunction and renal urate excretion in hyperuricemia patients. Surprisingly, hyperuricemic patients with graded levels of ABCG2 dysfunction, stratified by genotype for dysfunctional single nucleotide polymorphisms (SNPs), exhibited elevated urinary urate excretion and fractional excretion of urate (FE_{UA}) levels (332, 817). Furthermore, *Abcg2* KO mice showed increased renal urate excretion and serum urate levels and reduced intestinal excretion compared with wild-type mice. Thus ABCG2 dysfunction appeared to cause decreased extrarenal urate excretion (332, 817). It was shown subsequently that ABCG2 dysfunction can also impair renal excretion of urate in patients with lesser degrees of function (468).

The neurohumoral regulation of urate homeostasis involves angiotensin II, the sympathetic tone, insulin, and PTH (503). Alterations in volume status and/or dietary salt intake affect serum urate concentrations via modifications of its urinary excretion. Angiotensin II and epinephrine are the potential mediators (496, 833). The retention of urate by the kidney stimulated by insulin may play a crucial role in the associations between metabolic syndrome, hyperuricemia, and gout (115, 503). Elevated PTH levels also decrease urate excretion, in primary hyperparathyroidism and during pharmacological therapy for osteoporosis, which may be relevant for the association between gout and CKD (325, 503, 510). Finally, sex hormones appear to regulate urate transporters in mouse (309, 730), which could possibly explain why urate levels are higher in men compared with women (190, 633).

Here, we will address inherited disorders primarily involving renal urate transporters, resulting in hypouricemia. We will not discuss inborn errors of purine metabolism such as phosphoribosylpyrophosphate synthetase (PRPPS) superactivity (MIM no. 300661) characterized by congenital hyperuricemia and hyperuricosuria (575); nor familial juvenile hyperuricemic nephropathy (HNFJ1) (MIM no. 162000), a form of tubulointerstitial kidney disease caused by dominant mutations in the *UMOD* gene encoding uromodulin (Tamm-Horsfall protein), in which hyperuricemia is secondary to inappropriate tubular reabsorption of urate (low FE_{UA}) (162).

2. Renal hypouricemia

A) BRIEF CLINICAL DESCRIPTION. Renal hypouricemia (RHUC) is an autosomal recessive kidney disorder characterized by defective reabsorption of urate in the PT, resulting in increased urate clearance associated with hypouricemia. The first RHUC case was reported by Greene et al. in 1972 (261), but the molecular mechanisms and defective genes associated with this disorder were only identified 30 yr later. The majority of reported cases were initially reported in Japanese patients and non-Ashkenazi Jews (171, 191, 330, 331, 342, 396, 427, 726). However, recent studies suggested that RHUC is not restricted to East Asian populations, as the condition has been reported in various ethnic groups (e.g., Arab Israelis, Iraqi Jews, Caucasians, and Roma) and in geographically noncontiguous countries such as Macedonia, the United Kingdom, the US, the Czech Republic, and Spain (127, 226, 708).

The diagnosis of RHUC is based on hypouricemia (<119 μM or 2 mg/dl) with an increased fractional excretion of urate (FE_{UA} >10%) without any underlying renal or systemic diseases, such as RFS, or drug-induced tubulopathy. RHUC can be subdivided into two categories based on the molecular abnormalities (see below): renal hypouricemia type 1 (RHUC1) (MIM no. 220150) and renal hypouricemia type 2 (RHUC2) (MIM no. 612076). RHUC2 is char-

FIGURE 6. Handling of uric acid by the kidney. *A*: the classical four-component model of uric acid transport in the proximal tubule (PT), including glomerular filtration of urate, reabsorption of nearly all of the filtrated urate in the early PT, subsequent tubular secretion of up to half of this amount and final, postsecretory reabsorption of the majority of the secreted urate in the late part of PT. CD, collecting ducts; CNT, connecting tubule; DCT, distal convoluted tubule; TAL, thick ascending limb. *B*: molecular mechanism of urate reabsorption and secretion in PT. The reabsorption of urate involves the Na^+-dependent monocarboxylate anion transporters SMCT1 and SMCT2, which increase the intracellular concentration of anions and drive urate uptake via the apical exchange mediated by the urate transporter URAT1 and the organic anion transporters OAT4 and OAT10. GLUT9a is the exit pathway for urate at the basolateral membrane. The secretion of urate involves a basolateral entry in exchange with α-ketoglutarate (αKG), mediated by OAT1 and OAT3. The α-ketoglutarate gradient is provided by SLC13A3. On the apical side, the secretion of urate involves the ATP-driven efflux pumps ABCC4 and ABCG2/BCRP, as well as the electrogenic urate transporters NPT1 and NPT4. *C*: characteristics of renal hypouricemia (RHUC) type 1 and 2. ABCC4, ATP-binding cassette subfamily C member 4; ABCG2, ATP-binding cassette subfamily G member 2; BCRP, breast cancer resistance protein; GLUT9a, glucose transporter 9a; OAT, ornithine aminotransferase; SLC13A3, Na^+-dependent dicarboxylate transporter; SMCT, Na^+-coupled monocarboxylate transporter; NPT, Na^+-dependent phosphate transport protein; URAT1, urate transporter-1. [Adapted from Mandal and Mount (453) and Dinour and co-workers (171, 172).]

acterized by much lower serum urate levels and a FE_{UA} of ~150%, compatible with a total urate reabsorption defect, compared with RHUC1 (171) **(FIGURE 6*C*)**.

The majority of patients with RHUC remain clinically silent, and the disorder is often recognized during screening procedures of various unrelated diseases (700). Some patients may present nephrolithiasis, hypercalciuria, and hematuria. It is not completely clear why these manifestations are associated with RHUC, but a possible explanation is that a high rate of urate excretion results in stone formation followed by hematuria. Therapy is based on alkalinization of the urine and high fluid intake to prevent the precipitation of urate and the formation of urate nephrolithiasis. Indeed, elevated urinary concentration of urate, reduced urine ouput and low urine pH are major risk factors for the development of urolithiasis (190, 669, 700). Although not frequent, exercise-induced acute kidney injury (AKI) is a potential complication of RHUC (330, 396, 541, 669, 682, 700). The AKI typically develops after acute anaerobic exercise in previously healthy young adults and is associated with severe loin pain, nausea and vomiting, but without evidence of massive rhabdomyolysis. There is a marked male preponderance in such exercise-induced AKI (109). Contrast computed tomography of the kidneys demonstrates wedge-shaped defects, suggesting patchy renal vasoconstriction. The prognosis of exercise-induced AKI in patients with hypouricemia is good, with >80% of subjects recovering without dialysis therapy. The mechanisms of exercise-induced AKI associated with RHUC remain unclear; they could involve *1*) urate nephropathy resulting from an increase in urate production during exercise or *2*) renal reperfusion injury due to vasoconstriction caused by an exercise-induced increase in oxygen free radicals and a lack of urate, free radical scavengers (171, 330).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Hereditary renal hypouricemia is a heterogeneous, autosomal recessive disease that can be caused by mutations in the *SLC22A12* gene encoding the urate transporter URAT1 (RHUC1), or by mutations in the *SLC2A9* gene encoding the voltage-driven urate transporter GLUT9 (RHUC2).

I) Renal hypouricemia type 1 (RHUC1). Enomoto et al. (191) were the first to identify the urate transporter URAT1 and to demonstrate that mutational alterations in the gene *SLC22A12* (solute carrier gene family 22, 12th member; located at chromosome 11q13) coding for URAT1 are associated with RHUC1. URAT1 is a urate/anion exchanger, member of the organic anion transporter (OAT) family. It belongs to the amphiphilic solute carrier family (SLC22A) together with the organic cation transporters (OCT) (631, 671). The OAT family plays a crucial role in the transepithelial transport of various organic anions in the kidney. URAT1 is a membrane protein consisting of 553 amino acid residues with 12 putative transmembrane domains (TM). Similarly to other OAT family members, URAT1 has a large extracellular loop between transmembrane domain TM1 and TM2, and an intracellular loop between TM6 and TM7 (330, 396). The COOH-terminal end of URAT1 contains a binding motif for PDZ domain-containing proteins (190). The PDZ domain-containing protein PDZK1 interacts with URAT1 via this motif, and coexpression experiments demonstrated that URAT1 transport activity is increased by PDZK1/URAT1 interactions. PDZK1 may thus be as a scaffolding protein regulating the function of URAT1 (190). URAT1 is expressed specifically in the kidney where it is located in the apical membrane of PT cells. URAT1 transports urate from the lumen to the cytosol of the PT in exchange for monovalent organic anions, such as lactate and nicotinate. Pyrazinoate and several uricosuric agents such as probenecid and benzbromarone share the affinity for the URAT1 transporter (700).

The importance of URAT1 for the handling of urate was demonstrated by genetic analyses of Japanese patients with RHUC (191). These individuals harbour homozygous, heterozygous, or compound heterozygous loss-of-function mutations in the *SLC22A12* gene. Ichida et al. (330) showed that the p.W258X mutation predominates in Japanese patients with renal hypouricemia. This nonsense mutation produces a largely truncated protein (396). Expression of the mutant cDNA in *Xenopus* oocytes revealed that the truncated protein could not be targeted to the cell membrane, suggesting loss of function of the mutant protein (190). The p.W258X mutation is also predominant in Koreans with hypouricemia, indicating that the mutation originated in Asia (109) and expanded in the Japanese population either by founder effect or by genetic drift, or both (331). Studies in which mutant URAT1 proteins were expressed in *Xenopus* oocytes showed various degrees of residual transport activities, probably explaining the wide range of FE_{UA} values observed in RHUC patients (700). Ichida et al. (330) demonstrated a gene dosage effect of *SLC22A12* on C_{UA}/C_{cr} (urate clearance/creatinine clearance), correlating with the difference in serum urate levels. Serum urate levels were significantly lower and C_{UA}/C_{cr} was significantly higher in heterozygotes compared with healthy subjects. These changes were even more significant in homozygotes and compound heterozygotes (330)

Various types of *SLC22A12* mutations have been reported, including missense, nonsense, splice-site mutations, as well as short deletions and one gross deletion, and they are scattered along the 10 exons of the *SLC22A12* gene (856). Zhou et al. (856) recently summarized the clinical features and *SLC22A12* gene mutations reported up to now in RHUC patients. They showed that the frequency of the p.W258X mutation was very high (79.7%), as initially described by Ichida et al. (330). Patients with at least one p.W258X mutation were more likely to present urolithiasis, hematuria, or AKI (856). This mutation was predominant in patients of Jap-

anese and Korean origin, but was not found in patients of Chinese origin. The second most prevalent mutation, p.R90H, was found in patients of Japanese, Korean, and also Chinese origin. These two mutations were not observed in patients from other racial origins, including Czech Roma, Iraqi-Jews, and patients of European origin (856). Recently, Stiburkova et al. (710) suggested that not only loss-of-function mutations of *SLC22A12* but also dominant-negative effects cause RHUC1. Indeed, by coexpression and colocalization studies, they showed an accumulation and retention of the wild-type URAT1 protein in the ER by the p.G366R and p.R477H variants, which were detected in Czech family with an extremely rare coincidence of RHUC1 and autosomal dominant polycystic kidney disease (710).

Interestingly, *Urat1* KO mice exhibit a slightly higher FE_{UA} but do not develop significant hypouricemia (192, 310). The differences in plasma urate levels due to the loss of URAT1 in these mice are blunted by the degradation of urate in the liver. Indeed, in contrast to humans, mice possess the hepatic enzyme uricase (encoded by the *Uox* gene) which metabolizes urate to allantoin (311). Recently, a double KO mouse model for *Urat1* and *Uox* was developed, which may represent a suitable experimental model for RHUC type 1 (311). Administration of allopurinol was necessary to obtain plasma urate and urate excretion levels comparable to RHUC type 1 patients, since uricase deficiency in mice causes extreme hyperuricosuria and urate nephropathy (311, 825). Transgenic mice overexpressing *Urat1* showed no significant changes in plasma urate levels or urinary urate excretion, suggesting that URAT1 plays a less important role in the mouse kidney (383).

II) Renal hypouricemia type 2 (RHUC2). It was recently discovered that RHUC2 is caused by mutations in the *SLC2A9* gene (mapped to chromosome 4p15.3-p16), which encodes the urate transporter GLUT9 (172). GLUT9 is a member of the solute carrier family 2 (SLC2) of hexose facilitative transporters and consists of 12 transmembrane domains, a large extracellular loop between TM1 and TM2, and both NH_2- and COOH-terminal ends on the cytoplasmic side. Initially, GLUT9 was reported to be a glucose and/or fructose transporter (172). However, GWAS conducted to identify new genes in urate homeostasis showed significant association between variants in *SLC2A9* and serum urate levels (182, 366, 395, 405, 430, 778). Expression studies in *Xenopus* oocytes confirmed the role of GLUT9 as a urate transporter, with urate uptake significantly increased in GLUT9-expressing oocytes compared with control and URAT1-expressing oocytes (778). Increased urate uptake by overexpression of GLUT9 was also demonstrated in transfected human and mouse cells (99). The significance of GLUT9 function for human urate handling was further supported by the discovery of loss-of-function *SLC2A9* mutations in patients with RHUC (172, 173, 467).

The *SLC2A9* gene contains 14 exons and encodes 2 GLUT9 isoforms, a long (GLUT9a, 540 amino acids) and a short (GLUT9b, 512 amino acids) one, generated by alternative splicing and differing only in their NH_2-terminal region (26). The NH_2-terminal amino acids seem to play a role in their membrane trafficking and protein stability (51, 384). GLUT9a has a broad tissue distribution including the kidneys, liver, placenta, and leukocytes, whereas GLUT9b has been observed only in kidney and placenta (709). In the human kidney, GLUT9a is expressed at the basolateral membrane of PT cells **(FIGURE 6*B*)**, whereas GLUT9b was shown at the apical membrane of CD cells (384).

At least 10 different mutations in *SLC2A9* (including missense/nonsense mutations, 1 insertion, 1 deletion, and 1 duplication) associated with RHUC2 have been identified (172, 344, 467, 709). Most of these mutations have been functionally studied. However, interpretation of the pathogenicity of the identified variants remains difficult (629). Recently, Ruiz et al. (629) analyzed the function of known GLUT9 mutants using using [^{14}C]urate uptake assay and two-electrode voltage clamp in *Xenopus* oocytes. They demonstrated decreased urate transport by flux studies for most of the variants. None of the variants was permissive for glucose transport. Furthermore, two main categories of GLUT9 mutants were oberved: those harboring poor overall and cell-surface expression leading to low activity and those with preserved expression at the cell surface, but exhibiting decreased activity. Both mutant types are associated with a decreased urate transport ability, explaining the loss-of-function phenotype in RHUC patients (629).

Preitner et al. (579) investigated the renal phenotype of *Glut9* KO mice. Mice lacking GLUT9 are characterized by moderate hyperuricemia, massive hyperuricosuria, and early-onset obstructive nephropathy. However, the phenotype of these mice is modulated by the expression of *Glut9* in the liver, where it plays a role in the uptake of urate thereby facilitating its subsequent uricase-catalyzed degradation into allantoin (453). The liver-specific inactivation of *Glut9* led to severe hyperuricemia and hyperuricosuria, in the absence of urate nephropathy or structural changes in the kidney (579). Furthemore, the expression of GLUT9 in mouse kidney is different than in humans. In mouse, GLUT9 is mostly detected in the distal convoluted tubules (DCT) and connecting tubules, (CNT), with only limited expression in the PT (17, 579).

C. Disorders of Glucose Transport

1. Renal glucose handling

Glucose is a major source of metabolic energy for most cells of the body and is of critical importance in the brain. Glucose homeostasis is maintained by a complex interaction between gluconeogenesis in liver and kidney, absorption of

glucose by the kidney and intestine, as well as tissue storage and consumption. The kidney contributes to glucose homeostasis by reabsorption of virtually all the filtrated glucose at the PT level. Several transporters ensure the movement of glucose across PT cells, since cell membranes are impermeable to glucose. The rate-limiting step for PT reabsorption of glucose is its influx across the apical membrane via the Na^+-coupled glucose cotransporters SGLT1 and SGLT2 (295, 820, 821) **(FIGURE 7*A*)**. SGLT2 is a low-affinity/high-capacity cotransporter, which controls the bulk (90%) of glucose reabsorption and is expressed almost exclusively in the kidney, more particularly in the S1 segment of the PT (295, 820, 821). The remaining filtered glucose is reabsorbed by SGLT1, a high-affinity/low-capacity Na^+-glucose cotransporter, which is expressed more distally in the S2/S3 segment of the PT but is also strongly expressed in the intestine and which transports also galactose (295, 821). After the apical uptake, the transporters GLUT2 and GLUT1 facilitate the basolateral exit of glucose (113). The low-affinity glucose transporter GLUT2 works in synergy with SGLT2 in the S1 segment of the PT, whereas the high-affinity GLUT1 cooperates with SGLT1 in the S2/S3 segment (30, 459, 592) **(FIGURE 7, *A* AND *B*)**. This efficient and highly adaptive transport system ensures that glucose cannot be detected in the urine at below plasma glucose concentrations of 200 mg/dl. Glycosuria occurs when plasma glucose levels exceed the maximal reabsorptive capacity of the SGLT transport system, in the kidney PT, for known as the transport maximum for glucose, ranging from 260 to 350 mg/min/1.73 m^2 and corresponding to a plasma glucose level of 200 mg/dl (459, 490) **(FIGURE 7*C*)**.

Mutations in the gene encoding SGLT1 have been shown to cause glucose-galactose malabsorption, charcaterized by significant gastrointestinal dysfunction, but only mild renal glycosuria (752). Mutations in the gene encoding the GLUT2 transporter are associated with Fanconi-Bickel syndrome, a glycogen-storage disease with general PT dysfunction (484, 644). In this review we focus on familial renal glycosuria, involving the SGLT2 cotransporter.

2. Familial renal glycosuria.

A) BRIEF CLINICAL DESCRIPTION. Familial renal glycosuria (FRG) (MIM no. 233100) is an inherited disorder characterized by persistent glycosuria in the absence of both hyperglycemia and generalized PT dysfunction. The condition was first described by Hjärne in 1927 (301) and was historically classified into three different types (A, B, and O), based on the severity of glycosuria (88, 537, 602, 641). However, current molecular findings have enabled appropriate genotype-phenotype correlations in the vast majority of cases. Accordingly, a simpler and easier classification of FRG has been developed, based on the genetic defect (heterozygous, homozygous, or compound heterozygous *SLC5A2* mutations) (641). Glycosuria in FRG patients can range from <1 to >150 g/1.73 m^2 per day (855). No major clinical consequences are associated with FRG, which is considered to be a benign condition (641). However, clinical information is mainly based on case reports as an extensive evaluation of the phenotype associated with FRG in large cohorts is still lacking (88). Enuresis, polyuria, and a mild growth retardation and pubertal maturation delay were the only clinical manifestations observed during a 30-yr follow-up period of the originally described FRG patient (662). Other manifestations have occasionally been reported in severe forms of FRG (641), such as episodic dehydration and ketosis during pregnancy and starvation (537), the presence of autoantibodies without clinical evidence of autoimmune disease (149), an increased incidence of urinary tract infections (147, 149), as well as activation of the renin-angiotensin-aldosterone system (RAAS) secondary to natriuresis and possible extracellular volume depletion (87, 90). Moreover, selective aminoaciduria and even generalized aminoaciduria have been described in some cases, although it is not a general finding (88, 258, 452, 639). Interestingly, aminoaciduria has also been reported in patients with diabetes, and is most likely a consequence of the impaired glucose reabsorption in the PT rather than a primary defect (54, 641). Moreover, *Sglt2* KO mice, who mimic the glycosuric phenotype of patients with FRG, do not exhibit increased urinary excretion of amino acids (756). Hypercalciuria has also been reported in some patients with FRG, possibly indicative of further PT dysfunction (659, 662). Of note, it was recently shown that chronic loss of glucose in the urine did not protect from deterioration of the glucose tolerance in a large pedigree with FRG during a follow-up period of more than 10 yr (545).

B) GENETICS. FRG is caused by mutations in the *SLC5A2* gene, which is mapped to 16p11.2 and consists of 14 exons spanning 7.7 kb of genomic DNA. *SLC5A2* encodes the 672-amino acid Na^+-glucose cotransporter SGLT2 (642, 805, 806). *SLC5A2* was proposed as a major candidate gene for FRG in 1994 (368), and the first *SLC5A2* mutation in FRG was reported in 2000 by Santer et al. (643). Since then, molecular evaluation of small series of FRG patients (87, 90, 418, 452, 642, 796, 842, 843, 855) as well as several case reports supported the role of SGLT2 in this disorder (89, 216, 380, 388, 762, 840, 841, 844). More than 70 mutations, scattered throughout the *SCL5A2* gene, have been described up to now, including missense and nonsense mutations, small deletions (in-frame and frameshift), and splicing mutations (88, 418, 842, 855). Most of the reported mutations are missense mutations. The intron 7+5G>A (c.885+5G>A) mutation, reported in several unrelated pedigrees of different ethnic origins, might be a mutational hotspot (90, 642). Recently, Zhao et al. (855) reported another high-frequency mutation, a deletion in intron 7 resulting in abnormal splicing in *SLC5A2* gene, which might be another mutational hotspot. The mode of inheritance has long been debated, but FRG has now been shown to be inherited as a codominant trait with incom-

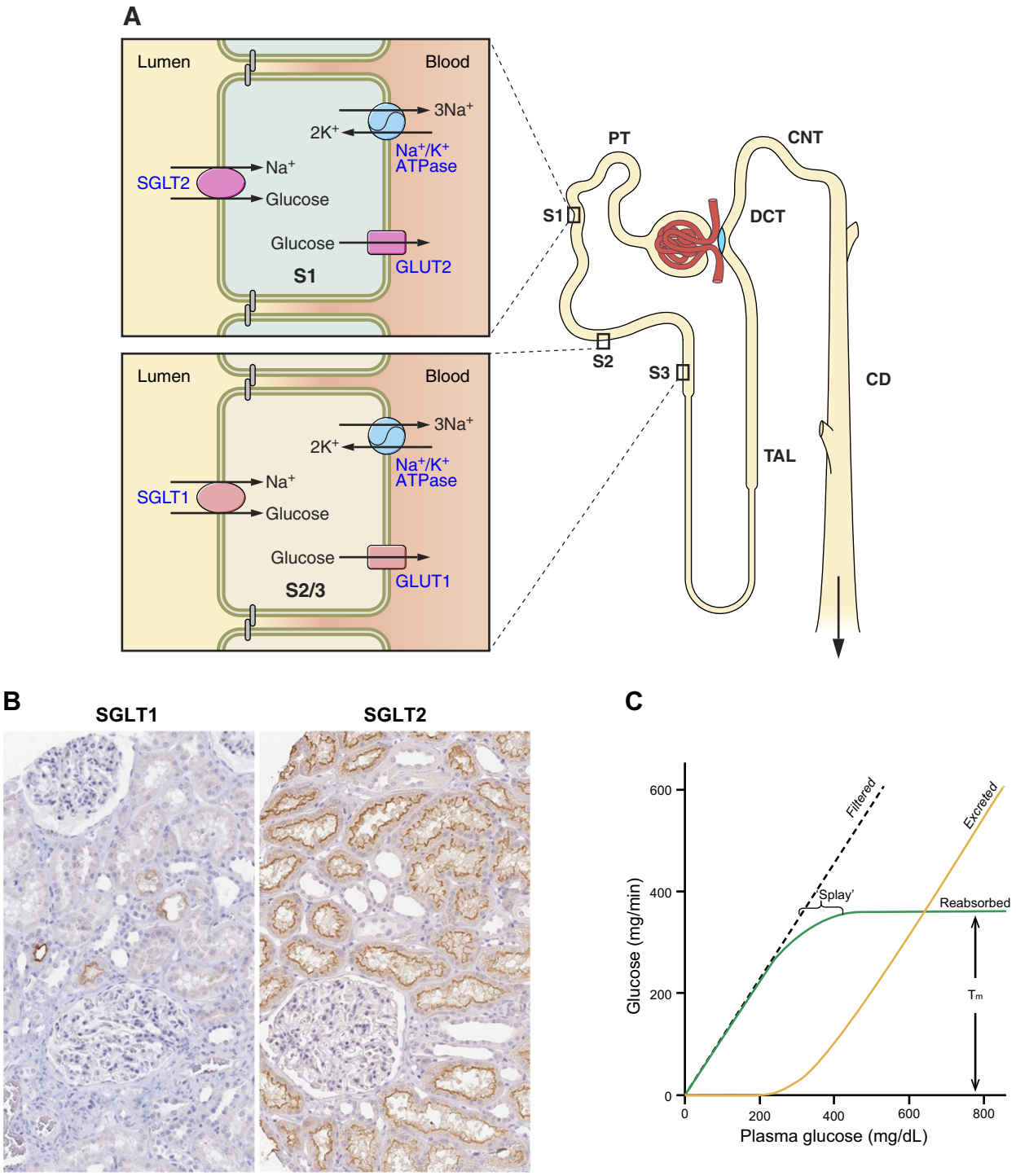


FIGURE 7. Glucose transport in the proximal tubule. *A*: molecular mechanisms of glucose transport. Glucose enters the cell via the apical Na^+-coupled glucose cotransporter SGLT2 that is expressed in the S1 segment of the proximal tubule (PT) and is responsible for the vast majority of glucose reabsorption. SGLT2 cooperates with the basolateral glucose transporter GLUT2. More distally, in the S3 segment of PT, the apical reabsorption of glucose occurs via the Na^+-coupled glucose cotransporter SGLT1, in synergy with the basolateral transport of glucose by GLUT1. *B*: segmental distribution of SGLT1 and SGLT2 in the PT segments of the human kidney. Note that SGLT2 is in fact much more abundant and located in the convoluted (S1-S2) parts of the proximal tubule. *C*: glucose handling in the kidney. The rate of glomerular filtration of glucose is proportional to the plasma glucose level. Glycosuria occurs when the transport maximum (Tm) for glucose in PT is approached, corresponding to a plasma glucose level of ~200 mg/dl. Image credit: Human Protein Atlas (www.proteinatlas.org), https://www.proteinatlas.org/ENSG00000100170-SLC5A1/tissue/kidney#img; https://www.proteinatlas.org/ENSG00000140675-SLC5A2/tissue/kidney#img.

plete penetrance (88, 641, 642, 842). Patients with mild glycosuria (<10 g/1.73 m^2 per day) are usually heterozygous for *SLC5A2* mutations, whereas homozygosity or compound heterozygosity is associated with severe glycosuria (>10 g/1.73 m^2 per day) (87, 88, 90, 642). However, a variable expressivity of mutations in FRG have been reported since patients with similar or identical mutations, especially in the heterozygous state, do not display similar degrees of glycosuria. Modifier genes, including other *SLC5* genes known to be expressed in the kidney and the involvement of which remains elusive, may explain this variable expressivity (88).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. The Na^+-glucose cotransporter SGLT2 accounts for the vast majority of glucose reabsorption in the PT. SGLT2 is a 672-amino acid protein, which belongs to the SLC5 family, also known as the Na^+ substrate symporter gene family. The SLC5 family compromises more than 230 members, including 12 members identified in humans that are expressed in tissues such as the small intestine, kidney, brain, muscle, and thyroid gland (820, 822). The SGLT members of the SLC5 family transport a vast variety of solutes ranging from sugars to inorganic ions. They share a common core structure of 13 transmembrane helices, although some members have one or two additional COOH-terminal helices. SGLT1 and SGLT2 both have 14 transmembrane helices with extracellular NH_2- and COOH-terminal domains (641, 819). Only a few studies investigated the functional consequences of *SLC5A2* variants (842, 843). All the *SLC5A2* variants tested exhibited lower transport activity upon reconstruction in cultured cells. The expression levels of the variants were significantly decreased, and some variants showed altered expression pattern with a loss of the typical punctuate membrane pattern seen in wild-type *SLC5A2* (842). These in vitro studies matched the evidence of a markedly lowered SGLT2 expression in PT cells in a kidney biopsy from a FRG patient (843).

Up to now, the mechanism of action of SGLT2 remains poorly understood. SGLT2 expresses only weakly in either transfected mammalian cells or *Xenopus* oocytes, rendering its characterization difficult. Coady et al. (128) recently identified an accessory protein, 17-kDa membrane-associated protein (MAP17), which is required for the normal function of SGLT2 in oocytes and mammalian cells. MAP17 was first identified as a protein with upregulated transcription in kidney, colon, breast, and lung cancer (392). In the PT, MAP17 interacts with the scaffolding protein PDZK1, which is linked to other transporters such as NHE3 and URAT1. Coady et al. (128) showed the physiological relevance of this MAP17-SGLT2 interaction studying a cohort of 60 patients with FRG in which they identified one patient homozygous for a splicing mutation in the MAP17 coding gene (*PDZK1IP1*), pointing to a genetic heterogeneity for FRG.

SGLT2 is localized to the brush-border membrane of the cells lining the early PT in mouse kidney. *Sglt2* KO mice exhibit glycosuria, polyuria, and increased food and fluid intake without differences in blood pressure, GFR, or plasma levels of Na^+ and K^+, and no significant increase in urinary excretion of other PT substrates such as amino acids (756). The genetic deletion of *Sglt2* in mice reduced blood glucose levels in streptozotocin-induced diabetes mellitus and attenuated glomerular hyperfiltration, but it did not prevent the increase of kidney growth or the rise of markers of kidney injury (758).

Pharmacological inhibition of SGLT2 has recently emerged as an innovative therapeutic strategy for the management of type 2 diabetes by increasing renal glucose excretion (30, 107, 150, 204, 242, 334, 465, 759, 760, 853). Compounds that enhance renal glucose excretion and promote weight loss, such as the natural occurring phenolglycoside phlorizin, have been known for a long time (105, 711). However, mechanisms of phlorizin-induced renal glycosuria were only recognized after the characterization of SGLT2 in the early 1990s (421). To date, three highly selective SGLT2 inhibitors, dapagliflozin, canagliflozin, and empagliflozin, have been approved for patient use. SGLT2 inhibitors have been demonstrated to reduce glycated hemoglobin (HbA1C), along with fasting and postprandial plasma glucose, as well as body weight and blood pressure in patient with type 2 diabetes (13). In addition to their antihyperglycemic properties, this emerging class of drugs shows renoprotective effects and cardiac benefits in patients with type 2 diabetes (150, 204, 760, 853). The SGLT2 inhibitors empagliflozin and canagliflozin have been evaluated in two major clinical trials, the EMPA-REG OUTCOME trial (551, 857) and the CANVAS Program (509), and showed clinically significant advantages over other antidiabetic drugs in protecting patients with type 2 diabetes against heart and kidney failure (760).

During the EMPA-REG OUTCOME trial and the CANVAS Program trial, the cardioprotective effect of SGLT2 inhibitors developed in the course of the treatment and can probably not be explained by the reduction of cardiovascular risk factors. Instead, they may be due to the metabolic properties of SGLT2 inhibitors: by increasing glucose excretion in the urine, these drugs induce a mild ketogenesis that in turn reduces blood glucose and insulin levels. The use of ketone bodies as an energy source might contribute to the cardiac benefit of SGLT2 inhibitors by improving the performance of cardiomyocytes (760).

A number of trials are currently ongoing to investigate whether the SGLT2 inhibition may also provide renal and cardiac benefits in a nondiabetic CKD setting. The renoprotective effects of SGLT2 inhibition are commonly explained by several pathways, including the tubular regulation of glomerular filtration. The SGLT2 inhibitors increase the

delivery of NaCl and fluid to the macula densa which reduces the GFR through tubuloglomerular feedback (TGF), thereby supressing the diabetes-induced hyperfiltration known to induce renal damage (152, 760, 853). However, the decrease of GFR induced by SGLT2 inhibitors may not necessarily reflect activation of the TGF. Indeed, micropuncture studies in a diabetic rat model have shown that increased reabsorption of solutes and water in the PT results in a reduced hydrostatic pressure in Bowman's space and in the PT in these diabetic animals compared with the nondiabetic rats (757). This reduced hydrostatic pressure will in turn increase the net filtration pressure, thereby contributing to the development of diabetic hyperfiltration. Inhibition of PT reabsorption allows the hydrostatic pressure in Bowman's space and in the PT to rise, thereby decreasing net filtration pressure and GFR. Interestingly, A1 adenosine receptor (A1AR) KO mice, which lack a functional TGF mechanism, still display pronounced glomerular hyperfiltration when diabetes is induced, indicating a TGF-independent mechanism in the development of diabetic hyperfiltration (198, 648). Moreover, inhibition of proximal sodium-linked glucose reabsorption by phlorizin in diabetic *A1ar* KO mice has been shown to reduce diabetes-induced glomerular hyperfiltration (649). Mathematical modeling proposes that effects of diabetes on GFR via TGF and hydrostatic pressure contribute each ~50% when both mechanisms are intact (280).

D. Disorders of Sodium Chloride Transport

1. Salt reabsorption processes

Salt (NaCl) is essential for life. The tight regulation of the body's Na^+ and Cl^- concentrations is so important that multiple mechanisms work in concert to control them. Na^+ and Cl^- are the primary ions in the extracellular fluid, including blood plasma. As such, they are central in a number of physiological mechanisms that regulate blood volume and blood pressure. The kidney is the main organ responsible for maintaining this vital balance. In general, active reabsorption of Na^+ generates the driving force for the passive reabsorption of water. Under physiological conditions, renal tubules are capable of reabsorbing 99% of filtered Na^+ and Cl^-. This is performed by a combination of several Na^+ and Cl^- channels and Na^+- or Cl^--coupled transport systems along the tubular segments of the nephron. Overall, the energy needed for the transport derives from the basolateral Na^+-K^+-ATPase, which is expressed in all tubular segments (180, 373).

The major part of the filtered Na^+ (~65%) is reabsorbed in the PT, via symporter and antiporter mechanisms. The latter is regarded as the most important Na^+ flux in the PT and is mediated by NHE3 (53, 506). The other main mechanism is the 1:1 Na^+-glucose cotransport that is mediated by SGLT2 (368, 839) **(FIGURE 8)**. The reabsorption of Na^+ and accompanying solutes creates a small transepithelial osmotic gradient, which drives water reabsorption primarily through the water channels AQP1, which are massively expressed in the apical and basolateral membranes of PT cells. Reabsorption of Na^+ together with uncharged solutes (e.g., glucose), HCO_3^- and water in the early PT establishes an electrochemical gradient that drives diffusion of Cl^- in the (mid-to-late) PT from the lumen to the peritubular interstitium, mainly via a paracellular pathway.

The TAL is responsible for reabsorbing 25–30% of the filtered NaCl load, which results in a diluted pro-urine as the TAL is essentially water impermeable (264). The apical entry of Na^+ is essentially mediated via the Na^+-K^+-Cl^- cotransporter (NKCC2) (230, 252), with a small contribution of NHE3 (~10% of the net Na^+ reabsorption in a microperfused rat study, see Ref. 687). A key feature of NKCC2 is the sensitivity to the loop diuretic furosemide. The net driving force for NKCC2 transport originates from low intracellular Na^+ concentration (263), which is established by the Na^+-K^+-ATPase activity at the basolateral membrane. Next, Cl^- exits the cell through the basolateral Cl^- channels ClC-Ka and ClC-Kb (5, 729), and via electroneutral K^+-Cl^- cotransporters (KCCs) (262) **(FIGURE 8)**. KCC4 has been detected at the basolateral membrane of the TAL (63, 243). The activity of NKCC2 and the apical renal outer medullary K^+ channel (ROMK), together with Cl^- efflux, generates a lumen-positive transepithelial voltage that drives paracellular transport of Ca^{2+} and Mg^{2+}.

The final 5–10% of the filtered Na^+ is actively reabsorbed by the apical Na^+-Cl^- cotransporter (NCC) and the epithelial Na^+ channel ENaC expressed in the distal nephron (187, 230, 771). Despite its short length (5 mm in humans), the DCT can be further subdivided into two distinct segments: DCT1 and DCT2 (717). NCC expression is confined to DCT1 and DCT2, while ENaC is expressed in DCT2 and in the downstream CNT and CD (135, 464) **(FIGURE 8)**. At the basolateral membrane, Na^+ is extruded by the Na^+-K^+-ATPase. Cl^- transport in the DCT1 is carried out by NCC and the Cl^- channel ClC-Kb at the apical and basolateral membranes, respectively. Furthermore, the basolateral membrane expresses KCC, and paracellular Cl^- transport has also been reported in the CD (318, 772). Additionaly, Cl^- is counter-transported with bicarbonate by pendrin in the intercalated cells of the CD (382, 560). Genetic or acquired defects in any of these transport systems, which are specific for individual nephron segments, lead to distinct salt-losing nephropathies. Here, we will consider the different renal genetic disorders affecting salt reabsorption.

2. Bartter syndrome

A) BRIEF CLINICAL DESCRIPTION. In 1962 Bartter et al. (36) reported two unrelated children with a new syndrome, characterized

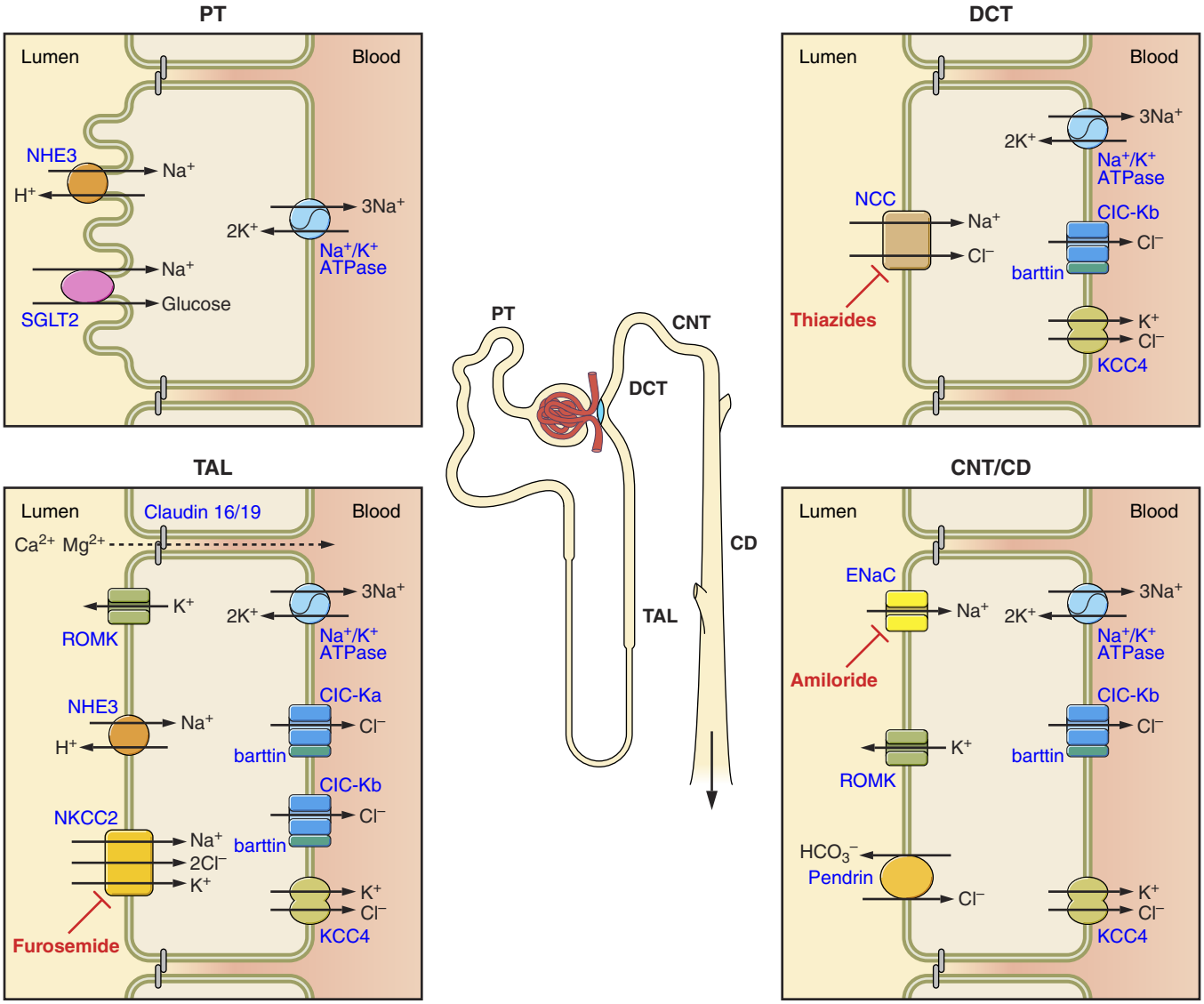


FIGURE 8. Sodium and chloride transport along the nephron segments. Reabsorption of Na^+ in the proximal tubule (PT) is mediated by the Na^+-H^+ exchanger NHE3 and coupled to glucose transport through SGLT2. In the thick ascending limb (TAL), Na^+ and Cl^- are essentially transported over the apical membrane by NKCC2, followed by efflux of Cl^- through ClC-Kb and Na^+ via the Na^+-K^+-ATPase. An estimated 10% of the apical uptake of Na^+ is mediated by NHE3. Barttin is an accessory protein regulating ClC-Kb function. The K^+ ions that enter the cell through NKCC2 are recycled back into the lumen via ROMK. Together, a lumen-positive transepithelial voltage is generated in the TAL that drives paracellular reabsorption of Ca^{2+} and Mg^{2+} through claudins 16/19. In the distal convoluted tubule (DCT), Na^+ and Cl^- are reabsorbed through the thiazide-sensitive NCC. The Na^+-K^+-ATPase and ClC-Kb, associated with its regulatory subunit barttin, mediate transport of Na^+ and Cl^- into the blood compartment. The Na^+ reabsorption in the connecting tubule (CNT) and collecting duct (CD) occurs via Na^+ entry through ENaC that is expressed at the apical membrane and the Na^+-K^+-ATPase that extrudes Na^+ at the basolateral side. The ENaC-mediated electrogenic Na^+ transport creates an electrical driving force for K^+ secretion via ROMK. Diuretics targeting Na^+ transport include furosemide for NKCC2, thiazides for NCC, and amiloride for ENaC. CD, collecting duct; ClC-Kb, chloride channel Kb; CNT, connecting tubule; DCT, distal convoluted tubule; ENaC, epithelial Na^+ channel; NCC, Na^+-Cl^- cotransporter; NHE3, Na^+-H^+ exchanger 3; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PT, proximal tubule; ROMK, renal outer medullary K^+ channel; SGLT2, sodium glucose transporter 2; TAL, thick ascending limb of the loop of Henle.

by hypokalemic metabolic alkalosis, renal K^+ wasting, hypertrophy and hyperplasia of the juxtaglomerular apparatus, and normotensive hyperaldosteronism. The disorder also featured increased urinary excretion of prostaglandins and high plasma renin activity (36). In the following decades, many similar cases and phenotypic variants have been described and included in a group of hypokalemic salt-losing tubulopathies, referred to as Bartter-like syndromes (270, 347). All these disorders are recessively inherited and associated with hypokalemia and hypochloremic metabolic alkalosis due to stimulation of the RAAS. However, they markedly differ in terms of age of onset, severity

of symptoms, presence of urinary concentrating defect, other electrolyte abnormalities (including hypomagnesemia), and magnitude of urinary Ca^{2+} excretion. Over the years, it became apparent that these tubular disorders may affect salt handling in distinct nephron segments, based on striking comparisons between the patient's symptoms and the effects of loop and thiazide diuretics affecting the TAL and DCT, respectively.

Based on clinical manifestations, the Bartter-like syndromes were grouped into two major groups: the antenatal Bartter syndrome (aBS), which can be associated or not with sensorineural deafness (SND); and the classic Bartter and Gitelman syndromes (cBS and GS, respectively) **(TABLE 3** and **FIGURE 9)**.

The aBS type 1 and type 2 (MIM nos. 601678 and 241200) are rare, life-threathening disorders characterized by massive polyuria that manifests in utero with the development of polyhydramnios and premature delivery in almost all cases. Affected neonates rapidly develop salt wasting, hypokalemic metabolic alkalosis, and profound polyuria (473, 583, 769). A majority of patients have hypercalciuria and nephrocalcinois, with increased risk for kidney stones (583). Mg^{2+} wasting is not a common finding in aBS (564). Failure to thrive and growth retardation are invariably observed (451, 583). The disorder is accompanied by markedly elevated urinary prostaglandin E_2 (PGE_2) excretion, and treatment with PG synthesis inhibitors effectively reduces clinical and biochemical manifestations (675). As patients with aBS failed to respond to loop diuretics such as furosemide, a defective NaCl reabsorption in the TAL was suspected (404). The two forms of aBS, due to mutations in the genes encoding NKCC2 or ROMK, are clinically and biochemically similar, with the exception of transient neonatal hyperkalemia that is only associated with mutations in *KCNJ1* (encoding ROMK) (210). Typically, hypokalemia in ROMK-deficient patients is less severe than that observed in NKCC2-deficient patients (564).

In 1995, Landau et al. (413) described a subtype of aBS associated with SND in five affected subjects from an inbred kindred. These patients show a severe salt wasting and fluid loss, and they most often develop progressive renal failure (346, 413). In 2001, Birkenhager et al. (55) detected inactivating mutations in a novel gene, *BSND*, in affected individuals. The gene encodes barttin, a regulatory beta-subunit of the basolateral ClC-Ka and ClC-Kb channels. This subtype of aBS was named aBS with SND, or type 4 BS (MIM no. 602522).

BS type 3, also referred to as cBS (MIM no. 607364), usually presents during infancy or early childhood, with a phenotype similar to the original description given by Bartter et al. (36), but without the prenatal onset and the

Table 3. *Genotypic and phenotypic characteristics of the different types of Bartter and Gitelman syndromes*

Disease	Inheritance	Gene	Protein	Affected Tubular Segment	Phenotype								Other
					Serum				Urine				
					Na^+	K^+	Mg^{2+}	Ca^{2+}	pH	Na^+	K^+	Mg^{2+}	Ca^{2+}	
Bartter type 1 (aBS)	AR	*SLC12A1*	NKCC2	TAL	–	↓	–	–	↑	↑	↑	↑	↑	Polyhydramnios, fetal polyuria, nephrocalcinosis
Bartter type 2 (aBS)	AR	*KCNJ1*	ROMK	TAL, DCT, CNT	↓	↑ (Initial)	–	–	↑	↑	↑	↑	↑	Polyhydramnios, fetal polyuria, nephrocalcinosis
Bartter type 3 (cBS)	AR	*CLCNKB*	ClC-Kb	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	
Bartter type 4 (aBS with SND)	AR	*BSND*	Barttin	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	Sensorineural deafness
Bartter type 4b (cBS)	AR	*CLCNKA-CLCNKB*	ClC-Ka/ClC-Kb	TAL+DCT	–	↓	–	–	↑	↑	↑	–	–/↑	Sensorineural deafness
Autosomal dominant hypocalcemia with Bartter	AD	*CASR*	CaSR	TAL+DCT	–	↓	–	↓	↑	↑	↑	–	–/↑	Nephrocalcinosis
Gitelman	AR	*SLC12A3*	NCC	DCT	–	↓	↓	–	↑	↑	↑	↑	↓	Chondrocalcinosis

↓, Decreased; ↑, increased; –, unchanged.

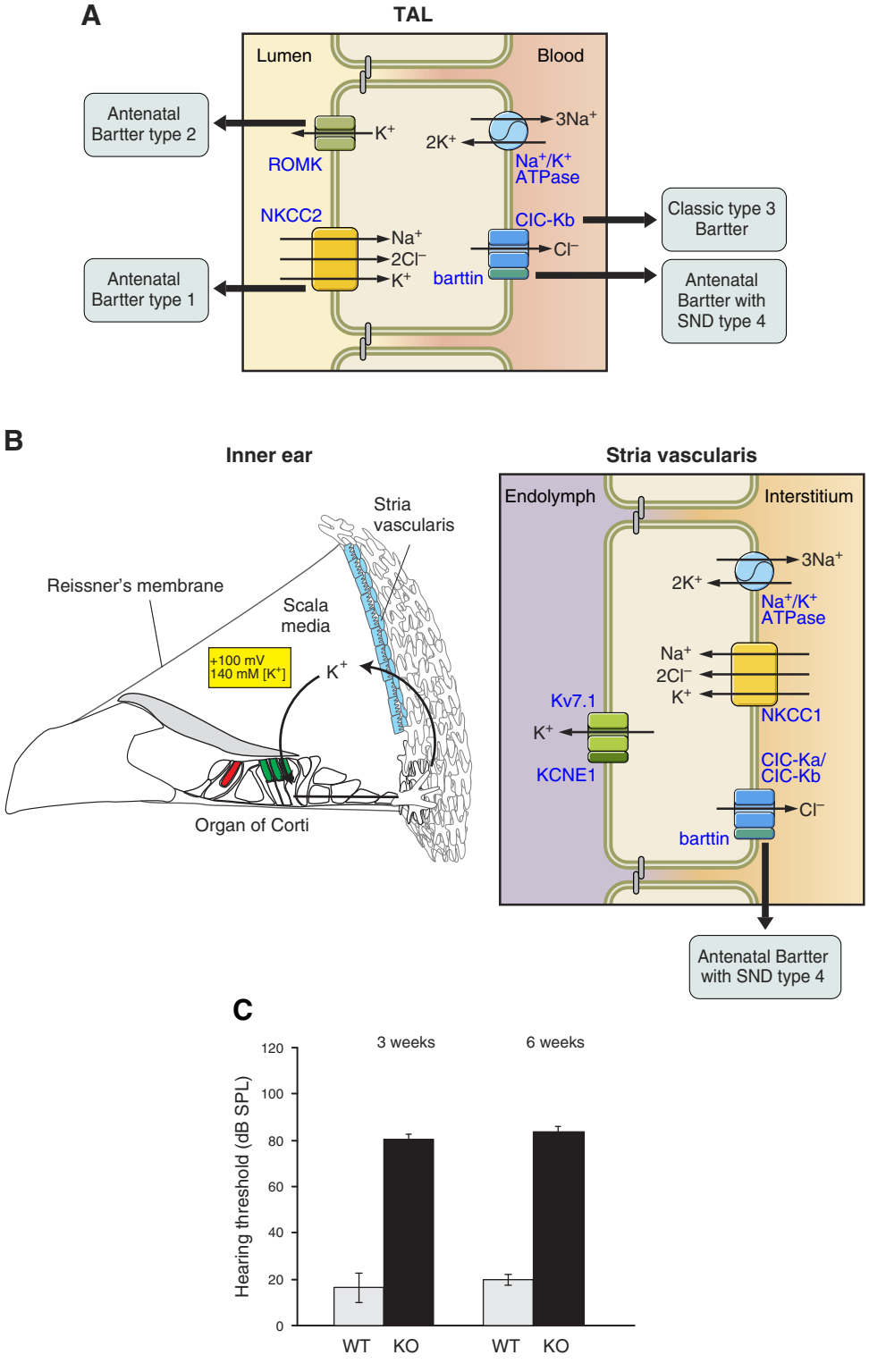


FIGURE 9. Various types of Bartter syndrome. *A*: in the TAL, Na^+ and Cl^- are transported over the apical membrane by NKCC2, followed by efflux of Cl^- through ClC-Kb and Na^+ via the Na^+-K^+-ATPase. Of note, barttin is identified as an accessory protein regulating ClC-Kb function. The K^+ that enter the cell through NKCC2 are recycled back into the lumen via ROMK. Mutations in either of the genes expressing these proteins result in the development of different types of Bartter syndrome. *B*: barttin is also expressed as a regulatory subunit for ClC-Kb and ClC-Ka in the inner ear and is thereby involved in sensory function. It is crucial for inner ear K^+ secretion. Patients with mutations in *BSDN*, encoding barttin, suffer from sensorineuronal deafness, as a result of barttin affecting both Cl^- channels in the inner. *C*: bar graphs depict the hearing thresholds in 3- and 6-wk-old wild-type (WT) and inner-ear-specific *Bsdn* knockout (KO) mice measured by auditory brainstem responses (ABR). ClC-Kb, chloride channel Kb; NKCC1 and NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; KCNE1, voltage-gated K^+ channel subfamily E regulatory subunit 1; Kv7.1, voltage-gated K^+ channel. [Adapted from Rickheit et al. (608), with permission from John Wiley and Sons.]

nephrocalcinosis seen in the aBS variant. The electrolyte abnormalities are usually severe at presentation, including hypokalemic alkalosis and increased plasma renin levels (564). Most patients with cBS show growth retardation and failure to thrive (45, 621, 667). Polyuria is not uniformly found in cBS. Lower urinary osmolality, either iso- or hyposthenuria, was only evidenced in approximately one-third of the patients, whereas some achieved urinary osmolality above 700 mOsm/kgH_2O (347). The persistance of such a urine concentrating ability suggests that patients have residual TAL function. This is further supported by the fact that only ~20% of patients have sustained hypercalciuria (564), and nephrocalcinosis was not detected in most cases (45, 621, 667).

In addition to these types of Bartter syndrome, gain-of-function mutations in the *CASR* gene encoding the extracellular calcium-sensing receptor (CaSR) cause autosomal dominant hypocalcemia with Bartter syndrome (previously named Bartter type 5) (MIM no. 601198) (294, 770, 800). In addition to clinical manifestations of Bartter syndrome, these patients present with hypocalcemia, reflecting the crucial role of the CaSR in divalent mineral homeostasis. The inherited disorders associated with the CaSR will be discussed in section III*E*.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Despite some overlapping features, the aBS group included disorders affecting the TAL, with furosemide-like manifestations, whereas the cBS group including GS is related to a defect in the DCT, with thiazide-like manifestations. A comprehensive classification of these salt-losing tubulopathies, based on the genetic, physiological, and molecular insights discussed below, provides a basis to understand the distinct phenotypes of these disorders **(TABLE 3)**.

I) Antenatal Bartter syndrome: type 1 (NKCC2) and type 2 (ROMK). Simon et al. (691) discovered that aBS type 1 (MIM no. 601678) is caused by loss-of-function mutations in the *SLC12A1* gene, located on 15q15-q21.1 and encoding NKCC2. This form of antenatal Bartter syndrome, also called hyperprostaglandin E syndrome (675), is one of the most severe forms that can be life-threatening for newborns when associated with fetal polyuria, polyhydramnios, and premature delivery (157, 538, 582, 676). Phenotypic variability among patients includes absence of hypokalemia and metabolic alkalosis within the first years, as well as an observed metabolic acidosis or hyponatremia (46). A late onset of the disease has been reported in two patients (aged 13 and 15 yr) harboring compound heterozygous mutations (580).

NKCC2 is a 121-kDa membrane protein comprising 12 putative transmembrane domains that form a transport pathway through dimerization of two homologous domains (702). It conducts the electroneutral transport of 1 Na^+, 1 K^+, and 2 Cl^- ions across the apical membrane of the TAL and thereby functions as the main salt reabsorption pathway in the kidney. Loop diuretics such as furosemide and bumetanide bind to portions of transmembrane domains 11 and 12, whereas portions of transmembrane domains 2, 4, and 7 are involved in ion transport (681). There have been numerous mutations in *SLC12A1* reported, mostly missense or frameshift, and they are essentially distributed throughout the entire encoded protein (4). The functional consequence of some of these mutations has been investigated in *Xenopus laevis* oocytes, demonstrating either impaired transporter function, reduced Na^+ affinity, or defective processing and misrouting of NKCC2 (3, 491, 580, 701). Recent studies have demonstrated that the phosphorylation and activity of NKCC2 is regulated by uromodulin, the most abundant protein in normal urine. Uromodulin is a GPI-anchored, ZP-domain protein encoded by the *UMOD* gene that is essentially expressed in the cells lining the TAL. In the TAL cells, uromodulin is trafficked to the apical membrane where, after proteolytic cleavage, it is released into the lumen to form multimeric filaments in the urine (162). Transient overexpression of uromodulin in heterologous cell systems increased the phosphorylation and activation of NKCC2 (507). *Umod* KO mice showed a discrete salt-losing phenotype with impaired response to furosemide and decreased levels of phosphorylated NKCC2 (507), whereas transgenic mice overexpressing *Umod* showed the opposite, i.e., higher level of phospho-NKCC2 and increased response to furosemide (750). The cross-talk between uromodulin and NKCC2 is potentially important for blood pressure regulation, as indicated by the association of common variants in the promoter of the *UMOD* gene with blood pressure and response to furosemide (162, 547, 750).

The aBS type 2 (MIM no. 241200), which can present with transient neonatal hyperkalemia, is caused by inactivating mutations in *KCNJ1*, which codes for ROMK (339a, 692). These mutations include missense and nonsense, as well as frameshift and deletions (294). Functional studies of mutated ROMK proteins showed that the loss-of-function originates from either an altered channel function or impaired plasma membrane abundance (563, 664, 668, 703). ROMK (also named Kir1.1) is an ATP-sensitive, inwardly rectifying renal K^+ channel that is critical for K^+ recycling in the TAL and K^+ secretion in the CNT and CD (219, 393, 420). ROMK channels are assembled from four subunits, each consisting of two transmembrane domains flanking a conserved loop that contributes to the pore and selectivity filter, and cytoplasmic NH_2 and COOH termini that contain regulatory and oligomerization domains (516a). In the TAL, ROMK plays a dual role as it supports NKKC2 transport activity essential for salt reabsorption, and also contributes to a positive transepithelial membrane potential important for paracellular reabsorption of Ca^{2+} and Mg^{2+} (264, 294, 803) **(FIGURE 8)**. Indeed, patients with Bartter syndrome (type 1 and type 2) often present with hypercalciuria, which increases the predisposition to nephrocalcinosis (583). Salt wasting, volume contraction, and metabolic alkalosis are explained by disrupted NaCl transport in the TAL, which in turn results in distal Na^+ delivery that drives ENaC function at the expense of increased K^+ and H^+ excretion.

The importance of NaCl handling in the TAL has been further demonstrated by screening members of the Framingham Heart Study (353). In that cohort, heterozygote carriers of inactivating mutations in *SLC12A1* and *KCNJ1* had significantly lower systolic and diastolic blood pressure, and a significant reduction in the risk of developing hypertension compared with non-carriers. The effects of the

carrier state on systolic and diastolic blood pressure at different age were similar to that of antihypertensive agents (353). Furthermore, Tobin et al. (745) showed that five polymorphisms in *KCNJ1* were associated with mean 24-h systolic or diastolic blood pressure. Two of these SNPs were located in the 3′ untranslated region and the remaining three SNPs were intronic. The strongest association was between the intronic variant (rs2846679) whose minor allele (frequency, 16%) was associated with a significant change in mean 24-h systolic blood pressure, after accounting for age, sex, and familial correlations. While the precise nature of the mechanisms by which variants in *KCNJ1* affect BP remains to be elucidated, these data suggest that these transporters involved in renal NaCl handing may exert a profound influence on blood pressure regulation in the general population (166).

Elevated PGE_2 levels are considered instrumental for most clinical abnormalities in Bartter patients. Prostaglandins increase K^+ secretion by activating the RAAS and are known to decrease Na^+ reabsorption in TAL, likely via inhibition of NKCC2 (379). Hence, treatment focuses on blocking the prostaglandin production with indomethacin, as it enhances the urinary concentrating ability by increasing the expression of NKCC2 in the TAL and the water channel aquaporin-2 in CD (203, 381). This is often started in infants of 4–6 wk old to reduce polyuria and hypercalciuria, improve hypokalemia, and normalize the plasma renin levels. However, care should be taken with newborns and prenatal indomethacin treatment as it might result in gastrointestinal complications, renal failure, and potentially hyperkalemia. Generally, a combination of indomethacin and K^+ supplementation results in management of the disease and stimulates development of growth and intellectual ability (583, 755).

Both *Slc12a1* and *Kcnj1* KO mice have comparable phenotypic characteristics to Bartter patients as they display hypokalemia in combination with extreme polyuria, hypercalciuria, and nephrocalcinosis (443, 725). Although 95% of these mice die within 2 wk of birth, micropuncture studies in the surviving mice demonstrated significantly impaired NaCl transport in the TAL (443). The development of another colony of *Kcnj1* KO mouse with higher survival rates, due to adaptative mechanisms and upregulation of Na^+ transport in the downstream DCT segment, offers more opportunity to study the pathophysiology of Bartter syndrome (448, 782).

In addition to the above-mentioned phenotype, patients with a transient form of aBS have been described (598). A recent study characterized this phenotype in six families and described a novel *X*-linked disease of severe polyhydramnios with prematurity and transient renal salt wasting (MIM no. 300971) that is caused by *MAGED2* mutations (410). The *MAGED2* gene (located on Xp11.21) encodes the melanoma-associated antigen D2 (MAGE-D2) protein that belongs to the MAGE family and has previously been reported in relation to cell-cycle regulation, apoptosis, and neurogenesis (33). Laghmani et al. (410) showed expression of MAGE-D2 in fetal and adult kidneys and found diminished expression of NKCC2 and NCC in a fetus with the disease, which might explain the severe renal salt wasting. Recently, Legrand et al. (422) detected mutations in *MAGED2* in 17 patients from 16 families in France. The *MAGED2* mutations explained 9% of cases of aBS, accounting for 38% of patients without identified genetic cause. The phenotype was variable and could also be observed in females (422). Further investigations are needed to understand the transient nature of the phenotype.

II) Classic Bartter syndrome: type 3. The cBS type 3 (MIM no. 607364) originates from mutations in the *CLCNKB* gene (located on 1p36) coding for the ClC-Kb Cl^- channel that mediates the basolateral Cl^- efflux from the cells lining the TAL and the DCT (400, 690). Patients harboring mutations in *CLCNKB* present a broad spectrum of clinical features that range from the aBS phenotype with polyhydramnios, isosthenuria, and hypercalciuria over to the classic BS phenotype with less impaired concentrating ability and normal urinary Ca^{2+} excretion, to a GS-like phenotype with hypocalciuria and hypomagnesemia (347, 400, 564, 621).

A relatively large number of *CLCNKB* mutations have been reported, which include frequent gene deletions but also nonsense, missense, small insertions/deletions, frameshift, and splice-site mutations (14, 80, 400, 530, 690). Interestingly, no genotype-phenotype correlations have been described yet. Similar to aBS, therapy involves a combination of indomethacin and high doses of KCl that is sometimes complemented with K^+-sparing diuretics to correct severe hypokalemia (45, 599). In cases with hypomagnesemia, supplementation with Mg^{2+} is recommended, but the correction is usually difficult (564). A followup study of patients harboring mutated *CLCNKB* showed persistently increased plasma renin levels as well as secondary hyperaldosteronism, and most patients developed proteinuria despite the control of other symptoms (45).

ClC-Kb belongs to the CLC family of chloride channels/exchangers, which includes nine isoforms in mammals (348). Both ClC-Kb and the closely related ClC-Ka isoform (encoded by *CLCNKA*) are expressed predominantly in the kidney, located on the basolateral membrane of the thin ascending limb (ClC-Ka only), TAL, and DCT cells, as well as in the intercalated cells of the collecting duct. Both ClC-Ka and ClC-Kb require the beta-subunit barttin to facilitate their insertion in the plasma membrane and generate Cl^- currents (195). Estevez et al. (195) showed that disease-causing missense mutations of *CLCNKB* resulted in significant reductions (or the loss) of ClC-Kb/barttin chan-

nel activity. Detailed studies of *CLCNKB* mutations in *Xenopus laevis* oocytes and HEK293 cells revealed two classes of mutants: nonconducting mutants associated with low total protein expression and partially conducting mutants with unaltered channel properties and ClC-Kb protein abundance (375). Thus inactivating mutations in *CLCNKB* affect the basolateral exit of Cl^-, which in turn reduces the reabsorption of NaCl in the TAL and DCT. The phenotypic variability of type 3 BS may thus be explained by the wide distribution of ClC-Kb (400, 564). Alternative pathways for Cl^- exit, which include ClC-Ka (348), KCC4 (772), or the Cl^-/H^+ exchanger ClC-5 (158) in the TAL, could partially compensate for ClC-Kb inactivation in the kidney.

Mice lacking *Clcnk2* (corresponding to *CLCNKB* in humans) have been generated that exhibited a Bartter syndrome phenotype, characterized by salt wasting, hypokalemia, and metabolic alkalosis (297). These mice did not show a natriuretic response to furosemide and had a significantly reduced response to thiazide. On the other hand, *Clcnk1* KO mice (corresponding to *CLCNKA*) exhibit polyuria but no signs of salt wasting or hypokalemic alkalosis (466). Together, this suggests that ClC-Kb is the critical Cl^- channel responsible for salt reabsorption in the TAL and DCT.

III) Antenatal Bartter syndrome with sensorineural deafness: type 4. Type 4 aBS (MIM no. 602522) is typically the most severe form of Bartter syndrome with early maternal polyhydramnios, prematurity, severe neonatal episodes of dehydration, and progressive renal failure (346, 347, 678). Moreover, these patients are deaf and have seriously impaired motor development and growth defect. An additional form of type 4 Bartter with SND (also termed type 4b, MIM no. 613090) is caused by coinciding mutations in *CLCNKA* and *CLCNKB* (532, 657).

The *BSND* gene (located on 1p32.3) consists of four exons. It encodes barttin, a 320-amino acid protein that contains two putative transmembrane domains and is expressed in the thin limb, TAL, and DCT in the kidney and in the stria vascularis surrounding the cochlear duct in the inner ear (55, 195). Barttin is a beta-subunit required for the expression and function of the Cl^- channels ClC-Kb and ClC-Ka (195, 785). Functional analysis of the identified *BSND* mutations revealed that missense mutations can either affect the channel properties of ClC-K/barttin channels despite normal membrane abundance or result in disturbed trafficking to the cell surface (343, 603, 660, 785). Hence, the severity of the disease is likely due to a loss of both ClC-K channels in all nephron segments. In contrast to patients harboring mutations in *SLC12A1* and *KCNJ1*, barttin-deficient patients exhibit only moderate and transient hypercalciuria and do not show nephrocalcinosis (347, 678). This could be due to defective NaCl transport in both the TAL and DCT, with divergent effects on urinary Ca^{2+} excretion that is somehow similar to a combined action of loop and thiazide diuretics. Barttin-deficient patients may show a severe Mg^{2+} wasting, caused by a defect in both the paracellular (TAL) and transcellular (DCT) pathways of Mg^{2+} reabsorption (347). Furthermore, a lack of diuretic response to furosemide and to hydrochlorothiazide was evidenced in one barttin-deficient patient, supporting a defect in both TAL and DCT (846).

Apart from the kidney, ClC-K channels are expressed in the inner ear, where they play a role in the secretion of K^+-rich endolymph required for the function of the inner hair cells (195, 608). Defective ClC-K/barttin channels will therefore eliminate this K^+ recycling in the inner ear and cause the SND **(FIGURE 9)**. A conditional *Bsnd* KO mouse model with specific deletion of barttin in the inner ear had no renal phenotype, but displayed congenital deafness (608). Importantly, none of the type 3 BS patients with *ClCKB* mutations is deaf because the function of ClC-Kb/barttin channels in the inner ear can be replaced by ClC-Ka/barttin. Only the disruption of barttin (195) or the combined loss of ClC-Ka and ClC-Kb (532, 657) results in a Cl^--recycling defect that lowers K^+ secretion in the stria vascularis to a pathogenic level.

While *Bsnd* KO mice die within a few days after birth (608), the generation of a KI mouse model that carries the R8L mutation provided in vivo evidence for the role of barttin (528). The mutant mice display Bartter syndrome characteristics like hypokalemic metabolic alkalosis and decreased salt reabsorption under a low-salt diet (528). A significantly reduced plasma membrane abundance of the CLC-K/mutant-barttin channels was observed in the TAL and distal nephron. The disease-causing R8L mutation was shown to result in ER-localized barttin that cannot recruit ClC-K to the plasma membrane in vitro (289). The KI mouse model was recently used to test a potential new drug, 17-allylamino-17-demethoxygeldanamycin (17-AAG), which is a 90-kDa heat shock protein inhibitor known to rescue ER-trapped proteins. Nomura et al. (527) demonstrated that treatment with 17-AAG enhanced the plasma membrane expression of barttin R8L and improved the electrolyte disturbances and hearing loss. New treatment regimes are highly valuable for the patients with type 4 BS, as the effect of indomethacin and K^+ supplementation on recovering growth and correcting electrolyte disorders is rather poor (346, 678).

3. Gitelman syndrome

A) BRIEF CLINICAL DESCRIPTION. Gitelman syndrome (GS) (MIM no. 263800) was first described in 1966 by Gitelman and co-workers as a familial disorder in which patients presented with hypokalemic alkalosis and a susceptibility to carpopedal spasm and tetany due to hypomagnesemia (244). The disease was long considered as a variant of Bartter syndrome with hypomagnesemia and hypocalciuria

(TABLE 3). In 1992 Bettinelli and co-workers concluded that GS could be distinguished from BS, based on low urinary Ca^{2+} excretion and frequent tetanic episodes (44). The dissociation of renal Ca^{2+} and Mg^{2+} handling in GS, together with the subnormal response of these patients to thiazides (720, 751), pointed to a primary defect in the DCT. GS is arguably the most frequent inherited tubulopathy detected in adults, with a prevalence of ~1 per 40,000 and a prevalence of heterozygous carriers in the Caucasian population estimated at ~1% (56).

Classically, GS has been considered as a mild variant of Bartter-like syndromes, often detected fortuitously during adolescence or adulthood. The GS patients are often asymptomatic or present with mild symptoms such as weakness, fatigue, salt craving, thirst, nocturia, constipation, or cramps (56). They may also present with growth retardation and short stature (247). Typical manifestations include low blood pressure, muscle weakness, carpopedal spasms, or tetanic episodes that are related to profound hypomagnesemia (138, 390, 401). Since Mg^{2+} ions increase the solubility of calcium pyrophosphate crystals and are important for the activity of pyrophosphatases, hypomagnesemia may promote the formation of calcium pyrophosphate crystals in joints and sclera, leading to chondrocalcinosis (586) and sclerochoroidal calcifications (71). Patients with GS have higher bone mineral density, similar to chronic thiazide treatment, which likely arises from increased renal Ca^{2+} reabsorption and a decreased rate of bone remodeling (518). K^+ and Mg^{2+} depletion result in prolonged QT interval in ~50% of the patients, which could lead to an increased risk for ventricular arrythmias (47, 213). The classical biochemical features of GS include hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. The presence of both hypomagnesemia and hypocalciuria is highly predictive for the diagnosis of GS (44).

The view that GS is a benign condition has been challenged by reports emphasizing the phenotype variability and the potential severity of the disease. GS is associated with a significant reduction in the quality of life, similar to that associated with congestive heart failure or diabetes (138). Manifestations such as early onset (before age 6 yr), growth retardation, invalidating chondrocalcinosis, tetany, rhabdomyolysis, seizures, and ventricular arrhythmia have been described (56). The phenotype of GS is highly heterogeneous in terms of age at presentation, nature/severity of biochemical abnormalities, and nature/severity of the clinical manifestations, not only between patients carrying different *SLC12A3* mutations, but also between affected family members (614).

Because GS is primarily caused by salt wasting, patients are encouraged to follow their propensity for salt consumption. Lifelong oral Mg^{2+} and K^+ supplementation is the mainstay of treatment (56, 390). In the presence of hypomagnesemia, Mg^{2+} supplementation should be considered first, because Mg^{2+} repletion will facilitate K^+ repletion (808). Many symptoms are improved by K^+ or Mg^{2+} supplementation or both, but there is no evidence correlating the severity of blood levels with the intensity of symptoms. In cases of persistent, symptomatic hypokalemia when supplements are not sufficient, the use of K^+-sparing diuretics (e.g., amiloride, spironolactone, potassium canrenoate, and eplerenone) can be useful (58, 130).

B) GENETICS. GS is caused by loss-of-function mutations in the *SLC12A3* gene, which codes for the thiazide-sensitive Na^+-Cl^- cotransporter NCC (424, 694). At present, over 250 disease-causing mutations have been identified in GS, of which a large part are missense mutations. GS is recessively inherited, and the majority of patients are compound heterozygous for different *SLC12A3* mutations. Of note, 15–20% of patients with GS are found to carry only a single mutation in *SLC12A3*, instead of being compound heterozygous or homozygous (423, 600, 614). It is likely that the second mutation resides either in gene regulatory fragments, 5′ or 3′ untranslated regions, or intronic sequences, or that there are large genomic rearrangements. Few studies have provided evidence for this hypothesis (440, 531, 768). The possibility of a heterozygous mutation in another gene should also be considered, as the clinical representation of the disease is highly heterogeneous. Mutations in *CLCNKB* have, for example, been reported in patients that have common characteristics of classic Bartter and Gitelman syndromes (345, 849). The distribution of ClC-Kb in both the TAL and DCT, and potential compensation by other Cl^- transporters, may probably explain these overlapping syndromes (347). In addition to *CLCNKB*, other genes participating in the complex handling of Na^+, Ca^{2+}, and Mg^{2+} in DCT are potential candidates to account for disease-causing or disease-modifying genes in GS (615). For instance, Belge et al. (38) showed that mice lacking parvalbumin, a cytosolic Ca^{2+}-binding protein that is selectively expressed in the DCT, had a phenotype resembling GS. These mice exhibited volume contraction, aldosteronism, and renal K^+ loss at baseline; an impaired response to hydrochlorothiazide; and higher bone mineral density. They demonstrated that these modifications were due to decreased expression of NCC, secondary to modifications in intracellular Ca^{2+} signaling in the DCT (38).

NCC belongs to the SLC12 family of electroneutral cation-chloride cotransporters that also contains the NKCC2 and KCC proteins (292). The identified *SLC12A3* mutations are spread throughout the entire protein. A limited number of mutations have been functionally analyzed for alterations in the plasma membrane expression and transport activity of mutant NCC. There appear to be different classes of *SLC12A3* mutations. First, they can affect the synthesis and target NCC for degradation, resulting in ablated plasma

membrane expression. Second, some mutants display impaired trafficking and membrane insertion, while they have normal function if they do reach the plasma membrane. Third, it is observed that NCC mutants reach the plasma membrane but show diminished transporter activity. And finally, there are splicing mutations that lead to truncated transcripts which are degraded before the translation process (144, 246, 614, 632).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. NCC includes 12 predicted transmembrane domains with intracellular NH_2 and COOH termini, and it likely functions as a dimer at the plasma membrane (145, 230, 231). The Cl^- affinity of NCC resides within the transmembrane 1–7 region, and the sensitivity for thiazide is located between transmembrane domain 8 and 12, whereas both areas appear to be involved in Na^+ affinity (494). The regulation of NCC involves posttranslational modifications including glycosylation, phosphorylation, and ubiquitination. NCC contains a large extracellular hydrophilic loop between transmembrane domain 7 and 8 holding two glycosylation sites (N404 and N424) that are essential for the function and membrane expression of the protein (307). Several *SLC12A3* mutations result in impaired glycosylation and defective trafficking of the protein to the plasma membrane (246, 632). The NH_2 terminus contains key phosphorylation sites, including T55 and T60 and S73 and S91, that stimulate NCC activity (546, 607). Indeed, a mutation in T60 is commonly found in patients with GS (434). The exact contribution of each phosphorylation site remains to be resolved, but the intracellular signaling cascade has largely been unraveled. Richardson et al. (607) have shown that activation of SPAK (STE20/SPS1-related proline-alanine-rich protein kinase) and OSR1 (oxidative stress responsive kinase) results in phosphorylation and activation of NCC **(FIGURE 10)**. This involves binding of a unique conserved COOH-terminal (CCT) domain within SPAK and OSR1 to the RFTI motif in the NH_2 terminus of NCC (607). The with-no-K (lysine) (WNK) family of serine-threonine kinases is found to play a role upstream in this process as they can induce phosphorylation of SPAK and OSR1 (495, 777). Here, the CCT domain is also required for binding and activation by the WNKs, which contain RFXV/I motifs as well. More details on the current model of NCC regulation will be discussed in section III*D4*.

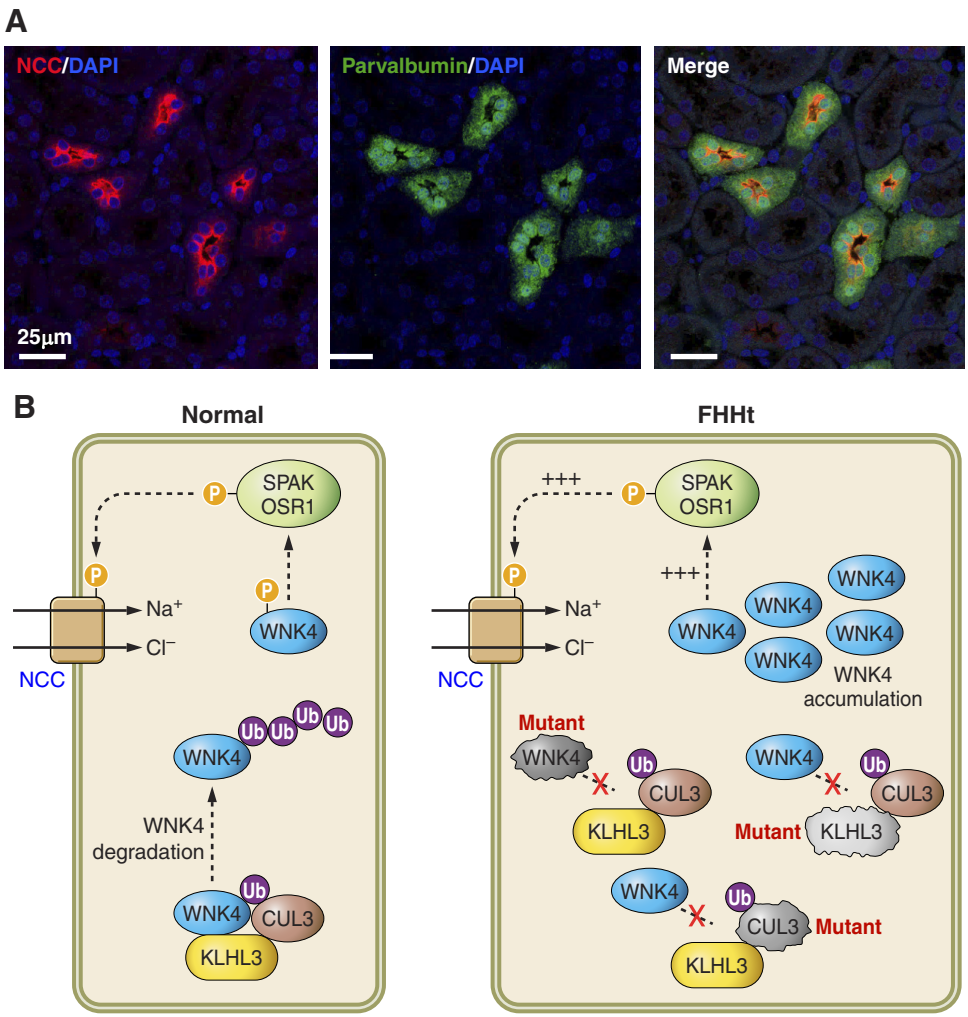


FIGURE 10. NCC-mediated Na^+ transport. *A*: immunohistochemical staining for NCC and the cytosolic protein parvalbumin in the epithelial cells lining the DCT. *B*: stimulation of WNK4 will phosphorylate SPAK/OSR1, which in turn activate NCC via phosphorylation and increased plasma membrane trafficking. On the other hand, the KLHL3/CUL3 complex can ubiquitylate the WNKs, thereby decreasing its expression and hampering the pathway that leads to NCC activity. In familial hyperkalemic hypertension (FHHt, also named Gordon syndrome), mutations in either *WNK4*, *KLHL3*, or *CUL3* result in increased WNK activation, which leads to enhanced NCC phosphorylation and activity, thereby explaining the hypertensive phenotype in FHHt patients. CUL3, cullin 3; FHHt, familial hyperkalemic hypertension; KLHL3, kelch-like family member 3; NCC, Na^+-Cl^- cotransporter; OSR1, oxidative stress responsive kinase; SPAK, STE20/SPS1-related proline-alanine-rich protein kinase; Ub, ubiquitin; WNK, with no lysine kinase.

The regulation of NCC by ubiquitination is a growing field of research. Ko et al. (391) were the first to suggest that NCC is modulated by ubiquitination, via a mechanism involving RasGRP1-mediated ERK1/2 activation. Further studies identified a role for the aldosterone-SGK1-Nedd4–2 pathway, which is also described to regulate ENaC activity (616). The E3 ubiquitin ligase Nedd4–2 (neural precursor cell expressed developmentally downregulated protein 4) was shown to interact with NCC and induce ubiquitination of the protein at the plasma membrane. This ubiquitination primes removal and degradation of NCC and thus reduces its activity. The activation of Nedd4–2 is known to result from phosphorylation by serum/glucocorticoid regulated kinase 1 (SGK1), which has an enhanced expression upon stimulation with the mineralocorticoid hormone aldosterone (50, 108, 697). Recent evidence suggests that phosphorylation and ubiquitination could have adverse effects on NCC: phosphorylated NCC had decreased ubiquitination (312), whereas WNK1 and WNK4 were shown to phosphorylate Nedd4–2 that ultimately promotes ubiquitination (296).

The pathophysiology of GS can be explained by the specific expression of NCC at the luminal membrane of the DCT, where it mediates the reabsorption of Na^+ and Cl^- (187) **(FIGURE 10)**. Loss of NCC function results in salt wasting, volume contraction, secondary hyperaldosteronism, and increased K^+ and H^+ secretion in the CD, resulting in hypokalemic metabolic alkalosis. As mentioned above, heterozygous carriers of mutations in *SLC12A3* from the Framingham Heart Study showed mean systolic blood pressure values that were below the entire cohort, with reduction in blood pressure being similar to values obtained with chronic thiazide treatment (353).

The importance of NCC as a highly-regulated, crucial player in NaCl handling by the DCT has been confirmed in different mouse models (773). Mice lacking NCC resemble a Gitelman phenotype with subtle changes in volume homeostasis, but clear alterations in the Ca^{2+} and Mg^{2+} balance (665). A later study showed that *Slc12a3* KO mice on a pure C57BL/6 background had a mild compensated alkalosis with increased levels of plasma aldosterone (442) and an increased sensitivity to develop hypokalemia when exposed to dietary K^+ reduction (499). These studies also demonstrated that loss of NCC results in hypertrophy of the distal tubule and that the observed hypocalciuria is caused by increased Ca^{2+} reabsorption in the PT (442). The latter hypothesis is supported by a study in which mice treated with thiazide diuretics developed hypocalciuria due to enhanced passive reabsorption of Ca^{2+} but independent of the distal expressed Ca^{2+} channel TRPV5 (transient receptor potential vanilloid 5) (522, 524). In addition, metabolic alkalosis is known to decrease renal Ca^{2+} excretion, which could also contribute to the observed hypocalciuria in Gitelman patients (64, 523). In contrast, the pathogenesis of hypomagnesemia observed in GS (and also after chronic thiazide administration) is likely due to a direct effect on DCT. Chronic thiazide treatment resulted in renal Mg^{2+} wasting and decreased expression of the epithelial Mg^{2+} channel TRPM6 (transient receptor potential melastatin 6) (524). TRPM6 is specifically expressed at the apical membrane of DCT1, the main site for active Mg^{2+} reabsorption (140, 780). Additionally, the TRPM6 mRNA levels were severely reduced in *Slc12a3* KO mice (524), which could reflect the atrophy of the DCT observed in these mice (442). This points towards a key role of TRPM6 in the development of hypomagnesemia in Gitelman patients, but further investigation is needed to unravel its exact underlying molecular mechanism.

4. Familial hyperkalemic hypertension

A) BRIEF CLINICAL DESCRIPTION. Although familial hyperkalemic hypertension (FHHt), also known as pseudohypoldosteronism type II (PHA2) (MIM no. 145260), was first described by Paver and Pauline in 1964 (556), Gordon delineated it as a new clinical condition, hence the term *Gordon Syndrome* (255, 256). It is characterized by hypertension, hyperkalemia, and metabolic acidosis; most patients have an early onset of the symptoms related to these electrolyte disturbances. The biochemical and clinical heterogeneity of the disease remains unclear due to the minimal number of families described so far. In general, hypertension appears in adult life and seems not prevented in patients in which the disease was diagnosed and treated before onset of hypertension (471). Untreated hypertensive individuals are at risk of developing complications related to the elevated blood pressure, like cardiac disease, renal impairment, and stroke. However, the electrolyte and blood pressure abnormalities can be corrected by treatment with thiazide diuretics, well-known inhibitors of NCC (419, 638, 673). This led to the initial idea that NCC plays a role in the pathogenesis of the disease, but no mutations in the gene encoding NCC have been identified in FHHt patients. Subsequent linkage analyses associated FHHt with several loci, and the disease was shown to have an autosomal dominant pattern of inheritance (176, 177, 457, 534).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. In 2001, disease-causing mutations in the *WNK1* and *WNK4* genes were identified in FHHt (814). These genes encode members of the WNK kinase family, WNK1 and WNK4, which are implicated in the regulation of epithelial transport of Na^+, K^+, and Cl^- in a variety of tissues (362).

WNK1 has two isoforms, namely, the long L-WNK1 isoform that is expressed ubiquitously, and the so-called kidney specific (KS) WNK1, whose expression is restricted to the kidney (114, 154, 718). The L-WNK1 isoform was shown to antagonize the inhibitory effect of WNK4 on NCC (836), thereby indirectly stimulating Na^+ reabsorp-

tion. In contrast, KS-WNK1 decreases NCC activity through antagonizing the L-WNK1 function (438, 718). L-WNK1 was also shown to activate ENaC via SGK1 phosphorylation (831), to inhibit ROMK (131, 437), and to decrease paracellular Cl^- transport via phosphorylation of claudin-4 (540).

The disease-causing *WNK1* mutations lead to large deletions in the first intron that have no effect on the final protein structure, but result in an overexpression of L-WNK1 in DCT and increased extrarenal expression of KS-WNK1 (153). Taken together, it is postulated that the net increase in L-WNK1 expression in the kidney will initiate FHHt pathogenesis via enhanced NCC activity (275). Interestingly, heterozygous *L-Wnk1*$^{+/-}$ mice showed a significantly reduced blood pressure compared with wild type (847), whereas mice KO for *Ks-wnk1* showed increased NCC activity in the DCT, as well as altered function of ROMK and decreased ENaC expression, in absence of hyperkalemic hypertension (276). Vidal-Petiot et al. (775) generated a mouse model with a heterozygous deletion of *Wnk1* that exhibited hyperkalemia, hypertension, and metabolic acidosis as a result of NCC activation. These mice had increased L-WNK1 expression and decreased ROMK expression in combination with unaltered ENaC function. Hence, the hypokalemia is suggested to be caused by inhibition of ROMK via L-WNK1.

The onset of FHHt by *WNK4* mutations was first considered to result from decreased inhibitory effect of WNK4 on NCC, as seen in *Xenopus* oocyte studies (815, 836). Furthermore, studies in oocytes showed that *WNK4* mutations increase the WNK4-mediated inhibition of ROMK (363), and an increased Cl^- permeability was demonstrated in MDCK cells (361, 834). Importantly, two independent groups generated KI mice harboring FHHt mutations that show phenotypes resembling FHHt as they exhibited increased blood pressure, hyperkalemia, and hypercalciuria (411, 838). This phenotype could be reversed by either treating the mice with thiazide or by backcrossing them with *Slc12a3*$^{-/-}$ mice (411, 838), which points towards a key role of NCC in FHHt. Interestingly, the *Wnk4*$^{-/-}$ mice have a Gitelman-like phenotype with mild hypokalemia, metabolic alkalosis, and hypomagnesemia but without hypocalciuria and hypotension (98). The K^+ wasting and normotension in the *Wnk4*$^{-/-}$ animals likely arise from increased ROMK and ENaC activities (98). A recent study by Takahashi et al. (723) postulates that WNK4, and not WNK1, is the major positive regulator of NCC, as they observed significantly decreased phosphorylated and total NCC levels despite an increase in WNK1 expression in their *Wnk4*$^{-/-}$ mice. Recently, it has been established that WNK4 exerts its action on NCC through the SPAK/OSR1 signaling cascade. Several mouse models have been generated with genetic alterations in WNK or SPAK/OSR1 to understand the role of these kinases in the regulation of NCC activity (274). While the exact physiological role of WNK1 and WNK4 is still a matter of debate, it is evident that these kinases are essential regulators of ion transport in the DCT, CNT, and CD. They were also shown to regulate the expression and function of ROMK and ENaC (274). Inhibition of these kinases would be a good target for regulating blood pressure (112, 590, 607).

Recent studies shed new light on the influence of dietary K^+ intake on blood pressure regulation through WNK signaling (736, 737, 781). They propose a link between the plasma K^+ concentration and NCC activity. Low dietary K^+ intake phosphorylates and activates NCC in the DCT despite high salt intake (737). Plasma K^+ levels can alter the intracellular Cl^- concentration via voltage-dependent Cl^- fluxes, which in turn modifies WNK activity. Piala et al. (566) demonstrated that Cl^- is able to bind the WNK1 catalytic domain, thereby inhibiting autophosphorylation and kinase activity. Hence, the DCT's ability to sense plasma K^+ levels is dependent on the WNK Cl^- responsiveness (737, 781). These studies support the role of WNKs in renal Na^+ and K^+ handling. The WNK activity is low when plasma K^+ levels are high. Following suppression of NCC, the Na^+ reabsorption occurs primarily along the CNT, not along the DCT. Na^+ reabsorption via ENaC is then exchanged for ROMK-mediated K^+ secretion **(FIGURE 11)**.

New insights into the mechanism of FHHt came from the identification of causative mutations in *KLHL3* and *CUL3* (73, 444). The encoded proteins kelch-like 3 (KLHL3) and cullin 3 (CUL3) function together in the cullin-RING E3 ligase complex that acts in the ubiquitin-mediated protein degradation pathway. Under normal conditions, the complex is able to interact and ubiquitinate the WNK kinases (724). Mutations in either *KLHL3* or *CUL3* disrupt the binding to WNKs, which subsequently leads to increased WNK1/WNK4 levels in the kidney that thereby control the activity of NCC and other ion transporters (539, 685, 784) **(FIGURE 10)**. The role of KLHL3 in the pathogenesis of FHHt was confirmed in vivo by generating *Klhl3*$^{R528H/+}$ KI mice that carry a mutation identified in FHHt patients. These mice have increased WNK1 and WNK4 levels, which indicates that both WNK1 and WNK4 are physiologically regulated by the KLHL3-mediated ubiquitination (719). Next, this group generated *Klhl3*$^{-/-}$ mice and demonstrated that lack of KLHL3 leads to increased WNK1 and WNK4 levels in the kidney, ultimately resulting in activation of the downstream OSR1/SPAK-mediated NCC phosphorylation (646). Of note, heterozygous *Klhl3*$^{+/-}$ mice did not exhibit a FHHt phenotype confirming that the previously observed phenotype in *Klhl3*$^{R528H/+}$ mice was caused by the dominant-negative effect of the *KLHL3* R528H mutation (646). As for *CUL3*, the mutations result in exon 9 skipping, which does not influence the binding of CUL3 to KLHL3, but it is suggested to disturb E3 ligase activity and

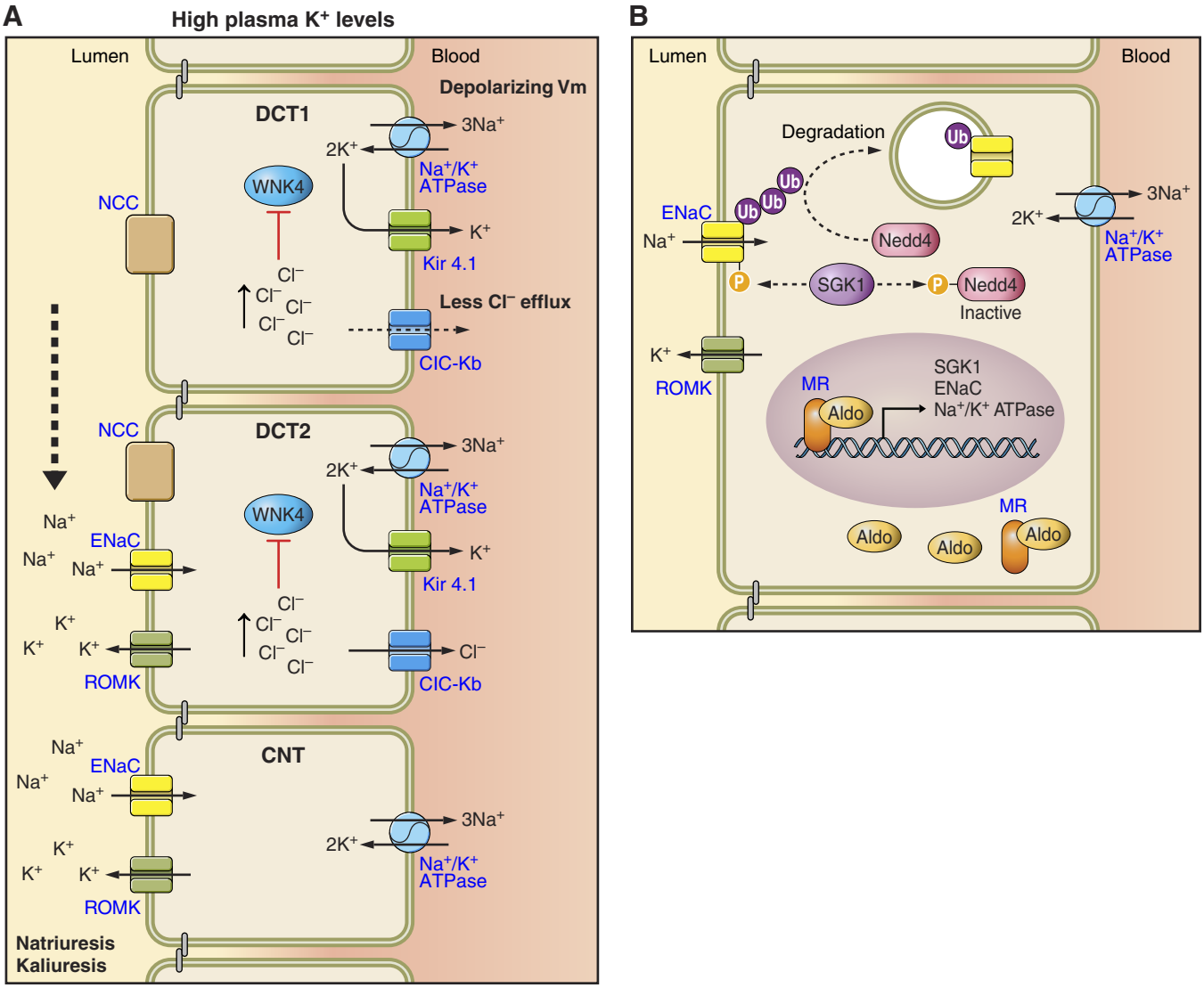


FIGURE 11. Mechanisms of sodium reabsorption in the distal nephron. *A*: the early part of the distal convoluted tubule (DCT1) is characterized by NCC expression at the apical membrane. Further downstream in the late DCT (DCT2) there is an overlapping expression of NCC and ENaC. Ultimately, ENaC is the sole Na^+ transport mechanism in the CNT and the CD. Here, ROMK colocalizes with ENaC and coordinates K^+ secretion. The K^+ channel Kir4.1 is expressed at the basolateral membrane where it extrudes K^+ into the blood compartment. Kir4.1 may also mediate the DCT's K^+ sensing which then controls intracellular Cl^- concentrations via affecting the membrane voltage. Increased plasma K^+ levels will depolarize the basolateral membrane, thereby reducing Cl^- efflux, and subsequent increased intracellular Cl^- levels reduce NCC activity via inhibition of the WNK pathway. *B*: aldosterone is identified as a key hormone binding to the intracellular mineralocorticoid receptor (MR) that is then translocated to the nucleus to induce the expression of ENaC, Na^+-K^+-ATPase, and SGK1. Activation of SGK1 leads to phosphorylation that inhibits the action of Nedd4, an ENaC interacting protein that controls the plasma membrane abundance of ENaC via ubiquitination and subsequent degradation. Aldo, aldosterone; ClC-Kb, chloride channel Kb; CNT, connecting tubule; DCT, distal convoluted tubule; ENaC, epithelial Na^+ channel; Kir4.1, inwardly rectifying K^+ channel; NCC, Na^+-Cl^- cotransporter; Nedd4–2, neural precursor cell-expressed developmentally downregulated gene 4–2; ROMK, renal outer medullary K^+ channel; SGK1, serum/glucocorticoid regulated kinase 1; Ub, ubiquitin; WNK, with no lysine kinase.

ubiquitination of at least a subset of KLHL3 targets (73, 784). Recently, a KI mouse model with specific targeting of exon 9 (*Cul3*$^{WT/\Delta 403-459}$) was generated that recapitulated the severe FHHt phenotype exhibiting hyperkalemia, hyperchloremia, and metabolic acidosis (666). Moreover, these mice showed a vascular phenotype that implies a stiffening of their arterial tree and suggests a vascular component contributing to the observed hypertension next to the salt retention mechanism in the DCT. Altogether, the identification of these novel proteins has given more insight into the renal regulation of salt balance and specifically the function of the distal part of the nephron, which might ultimately contribute to development of new drugs targeting high blood pressure in the general population.

5. Liddle syndrome

A) BRIEF CLINICAL DESCRIPTION. Another disorder characterized by early onset of hypertension is Liddle syndrome (MIM no. 177200), first described in 1963 by Liddle et al. (431). In addition to severe hypertension, patients suffer from hypokalemic metabolic alkalosis, reduced plasma renin activity, and diminished aldosterone secretion (70, 431, 799). Patients are most often treated with amiloride or triamterene, which normalizes their blood pressure and hypokalemia, but has only minimal effects on plasma aldosterone level or plasma renin activity (70, 351, 431). The effectiveness of this treatment had put the amiloride-sensitive Na^+ channel ENaC, located in the distal nephron, as a logical candidate gene for this disease.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Analyzing the original Liddle's pedigree, Shimkets et al. (686) showed complete linkage to the *SCNN1B* gene encoding the β-subunit of ENaC on chromosome 16p13–12. ENaC is comprised of three homologous subunits: α, β, and γ which act together to confer its low Na^+ conductance and its high selectivity for Na^+ and amiloride (91). In this pedigree and in other unrelated kindreds, a premature stop codon, a frameshift mutation, and other deleterious mutations were found, all located in the last exon of the gene encoding for the intracellular COOH-terminal domain of the β-subunit (351, 686). These dominantly inherited mutations were shown to be gain-of-function, with an increased amiloride-sensitive Na^+ current after transfection of the corresponding mutant subunits together with α and γ wild-type subunits. Other point mutations affecting the *SCNN1G* gene coding for same region of the γ-subunit of ENaC have also been found to cause Liddle syndrome (285).

The ENaC channel is responsible for Na^+ reabsorption across several epithelial tissues. Due to its apical localization in the cells lining the CNT and CD of the kidney, ENaC is regarded as a key player in the final regulation of Na^+ reabsorption (91, 123, 221, 234, 281). Mice that lack α-ENaC exhibit perinatal lethality due to impaired lung epithelial function (326), suggesting that the β- and γ-subunits alone are not sufficient for ENaC function. In comparison, the *Scnn1b*- and *Scnn1g*-null mice die within 48 h after birth because of an early renal dysfunction (34, 474), while low residual ENaC activity in the airway epithelia is likely due to the α-subunit.

Comprehensive studies have shown the mechanism by which the truncation or alteration of a conserved motif (PPxxY) in the COOH terminus of the β and γ subunits alters the function of ENaC (655, 698). Normally, a specific interaction between this PY motif and cytosolic proteins (Nedd4 isoforms 1 and 2, and other related WW proteins) leads to ubiquitination and then degradation of part of the newly synthetized subunits (626). Thus cell surface expression of ENaC is in part controlled by ubiquitination which is regulated by Nedd4–2 and SGK1 **(FIGURE 11)** (704). Both truncation or punctual mutations of the PY motif abrogate the Nedd4-mediated ubiquitination and increase surface expression of the mutant ENaC proteins, thus increasing the number of Na^+ channels in the apical membrane (2, 211). In turn, this promotes Na^+ reabsorption by the distal nephron, expansion of plasma volume, and hypertension which inhibits the secretion of renin and aldosterone. The fact that only one heterozygous mutation of either *SCNN1B* or *SCNN1G* is sufficient to lead to the pathology is probably due in part to the multimeric arrangement of the channel.

Shi et al. (684) generated *Nedd4–2* KO mice that displayed higher blood pressure than their wild-type littermates and had increased renal expression of all ENaC subunits, supporting the importance of Nedd4–2 in ENaC function and blood pressure regulation. Recently, an inducible kidney-specific *Nedd4–2* KO mouse model was developed, demonstrating the role of Nedd4–2 in the adult kidney tubules (623). These conditional KO mice maintain a normal Na^+/K^+ balance but develop increased blood pressure and hypercalciuria under high-Na^+ diet. They showed increased protein levels of β-ENaC and γ-ENaC but also of ROMK and of total and phosphorylated NCC in the kidney (623). The fact that Nedd4–2-dependent ubiquitination might also regulate NCC function is highly relevant when considering that mutations in *KLHL3* and *CUL3* are also linked to hypertension (73, 444).

Further evidence derived from the generation of KI mice carrying the *Scnn1b* R566stop mutation that displayed low plasma aldosterone and a salt-induced Liddle phenotype (576). Bertog et al. (42) found that the ENaC-mediated Na^+ transport in the colon of these mice was enhanced, together with an increased responsiveness to aldosterone. In addition to the colonic effect, it was recently demonstrated that DCT2/CNT is the primary nephron segment responsible for the disease-causing gain-of-function effect of the ENaC mutation (514). It will be interesting to unravel hormonal and/or molecular factors that regulate ENaC in that segment. Similarly, the recent discovery of a functional interaction between ENaC and NCC in the DCT also needs further exploration (487, 829).

6. Pseudohypoaldosteronism type 1.

A) BRIEF CLINICAL DESCRIPTION. Type 1 pseudohypoaldosteronism (PHA1) is a rare form of mineralocorticoid resistance characterized by neonatal renal salt wasting, failure to thrive, and dehydration. It is associated with hyponatremia, hyperkalemia, and metabolic acidosis, despite extremely high values of plasma renin and aldosterone (8, 850). There are two different clinical forms of PHA1: *1*) an autosomal dominant form, in which mineralocorticoid resistance is restricted to

the kidney, and 2) an autosomal recessive form, where mineralocorticoid resistance is systemic and salt loss occurs in multiple organs (288). Generally, treatment of PHA1 patients focuses on the replenishment of salt and water loss by salt supplementation, and on correction of hyperkalemia and acidosis. The correction of the generalized form usually requires high doses of Na^+ together with ion exchange resins and dietary changes to control hyperkalemia, throughout life (40, 287).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. *I) Autosomal dominant type 1 pseudohypoaldosteronism*. The renal, autosomal dominant PHA1 (MIM no. 177735) is caused by mutations in the *NR3C2* gene encoding the mineralocorticoid receptor (MR) (236, 585, 609). It is a mild form of the disease, and the most frequent. Treatment with Na^+ supplementation relieves patients from symptoms by 1–3 yr of age. Mutations are located throughout the *NR3C2* gene and result in a truncated or inactive MR that does not bind aldosterone, thereby hampering the aldosterone-induced transcription of hormone-responsive genes (137, 454, 609, 645) **(FIGURE 11)**. While haploinsufficiency is able to cause the disease, there are also reports of dominant-negative effects on the wild-type MR since the receptor functions as a dimer in transcription regulation (202, 237). Recent insight into the location and functional consequences of the *NR3C2* mutations revealed individual promoter-dependent effects on gene expression (202). This could explain the phenotypic differences that are observed in PHA1 patients; future studies in large patient groups should clarify any genotype-phenotype correlations.

The role of the MR in the maintenance of the Na^+ balance was demonstrated in the homozygous *Nr3c2* null mice that develop PHA1 symptoms within the first week after birth and later die from dehydration as a result of renal Na^+ loss (41). Conditional KO mice that lack expression of MR in the CNT and CD merely develop a PHA1 phenotype upon a low-salt diet (622). This highlights the refined mechanism of adaptation of the kidney tubule, and also the complex aldosterone signaling that likely regulates renal Na^+ transport through different pathways.

II) Autosomal recessive type 1 pseudohypoaldosteronism. The systemic, autosomal recessive variant of PHA1 (MIM no. 264350) is associated with ENaC loss-of-function mutations (103). Patients often have more severe symptoms due to disturbed Na^+ transport in all organs that express ENaC including lung, kidney, colon, and salivary glands (69, 378, 535, 650). Hence, the PHA1 phenotype includes serious respiratory tract illnesses and inflammation of eccrine sweat glands due to the high sweat salt concentration. Immediate diagnosis of the disease is essential to prevent neonatal death. If detected, the autosomal recessive PHA1 is a life-long disease that needs extensive salt supplementation in combination with K^+-lowering ion exchange resins (185, 286). Additional symptomatic treatment is often needed to relieve respiratory tract disturbances and improve the skin phenotype in these patients. In contrast to Liddle syndrome, mutations are found in all three ENaC subunits encoded by *SCNN1A*, *SCNN1B*, and *SCNN1G* (103). These are mainly frameshift or nonsense mutations that lead to truncated proteins or complete loss of ENaC expression. Loss-of-function mutations have been found in affected patients being either homozygous, in consanguineous families, or composite heterozygous (103, 715). Functional characterization of some identified missense mutations demonstrated reduced ENaC activity due to altered open probability or ion selectivity, highlighting a conserved His-Gly region in the cytoplasmic NH_2 terminus that is critical for ENaC function (267, 268, 376, 377). Recent cases have been reported that showed phenotypically distinct forms of systemic PHA1. Heterozygote carriers of a *SCNN1A* S562P missense mutation, originally identified in homozygous patients with autosomal recessive PHA1, show a subclinical salt-losing phenotype without additional features (610). A homozygous missense mutation (S243P) in *SCNN1A* that was associated with partial loss of ENaC channel activity resulted in a transient PHA1 phenotype in the premature infant, that could be corrected easily with salt supplementation stopped after 6 mo (175). These cases broaden the clinical spectrum of PHA1 and support further genetic screening as no clear genotype-phenotype correlation has been established so far (611, 850).

As mentioned above, the *Scnn1a*, *Scnn1b*, and *Scnn1g* KO mice all die soon after birth, and present with renal phenotypes similar to those observed in PHA1 patients (34, 326, 474). This did not allow detailed analysis of ENaC deletion specifically in the kidney and/or during adulthood. Hence, several transgenic mice with specific deletion of αENaC in renal tubules or only in the CNT were generated (119, 561). While CNT-specific *Scnn1a* KO mice only developed a mild PHA1 phenotype under low-salt diet, the renal tubule-specific *Scnn1a* KO model mimicked the severe PHA1. They suffered from severe hyperkalemia and decreased K^+ excretion, which could be rescued by high dietary Na^+ or low K^+ intake (561). A similar phenomenon was observed in nephron-specific *Scnn1b* KO mice (67). In contrast, the severe PHA1 phenotype cannot be rescued in nephron-specific *Scnn1g* KO mice upon high-Na^+ and/or low-K^+ diet (68). Hyperkalemia could only be avoided by preventive treatment with a K^+-deficient diet that restored NCC activity in these mice (68). This suggests that γ-ENaC is required for renal K^+ handling, and it supports the link between plasma K^+ levels and NCC regulation. A better understanding of the genetic background and biological outcome of PHA1 will be valuable to address blood pressure disturbances in the general population.

E. Disorders of Calcium Transport

1. The integrative network of renal calcium regulation

The Ca^{2+} balance depends on the interplay of intestinal absorption, renal excretion, and bone remodelling. Over 99% of the total body Ca^{2+} content is stored in the skeleton where it functions both as an essential element for skeletal strength, as well as a dynamic supply for the maintenance of circulating Ca^{2+} levels. Part of the non-bone Ca^{2+} is bound to calcium-binding proteins including albumin and globulin in plasma, and calmodulin and other calcium-binding proteins in the cells. Importantly, the free ionized Ca^{2+} needs to be tightly maintained within physiological range (1.10–1.35 mM) to prevent Ca^{2+} toxicity. This is regulated by a hormonal negative feedback mechanism involving the hormones PTH, fibroblast growth factor 23 (FGF23), and 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] that regulate Ca^{2+} transport processes in the intestine, kidney, and bone **(FIGURE 12)** (766). In short, a decline in plasma Ca^{2+} levels will stimulate the release of PTH via activation of the CaSR in the parathyroid gland (606). Subsequently, PTH regulates Ca^{2+} transport processes in bone and kidney and stimulates the production of $1,25(OH)_2D_3$ (505). $1,25(OH)_2D_3$ can enhance the expression of Ca^{2+} (and phosphate) transporters in kidney, bone, and intestine (118). In addition, $1,25(OH)_2D_3$ stimulates the production of FGF23 in bone, a key hormone in phosphate homeostasis. FGF23 also controls Ca^{2+} balance by regulating the expression of PTH in the parathyroid gland and has a negative feedback loop to inhibit $1,25(OH)_2D_3$ production (59).

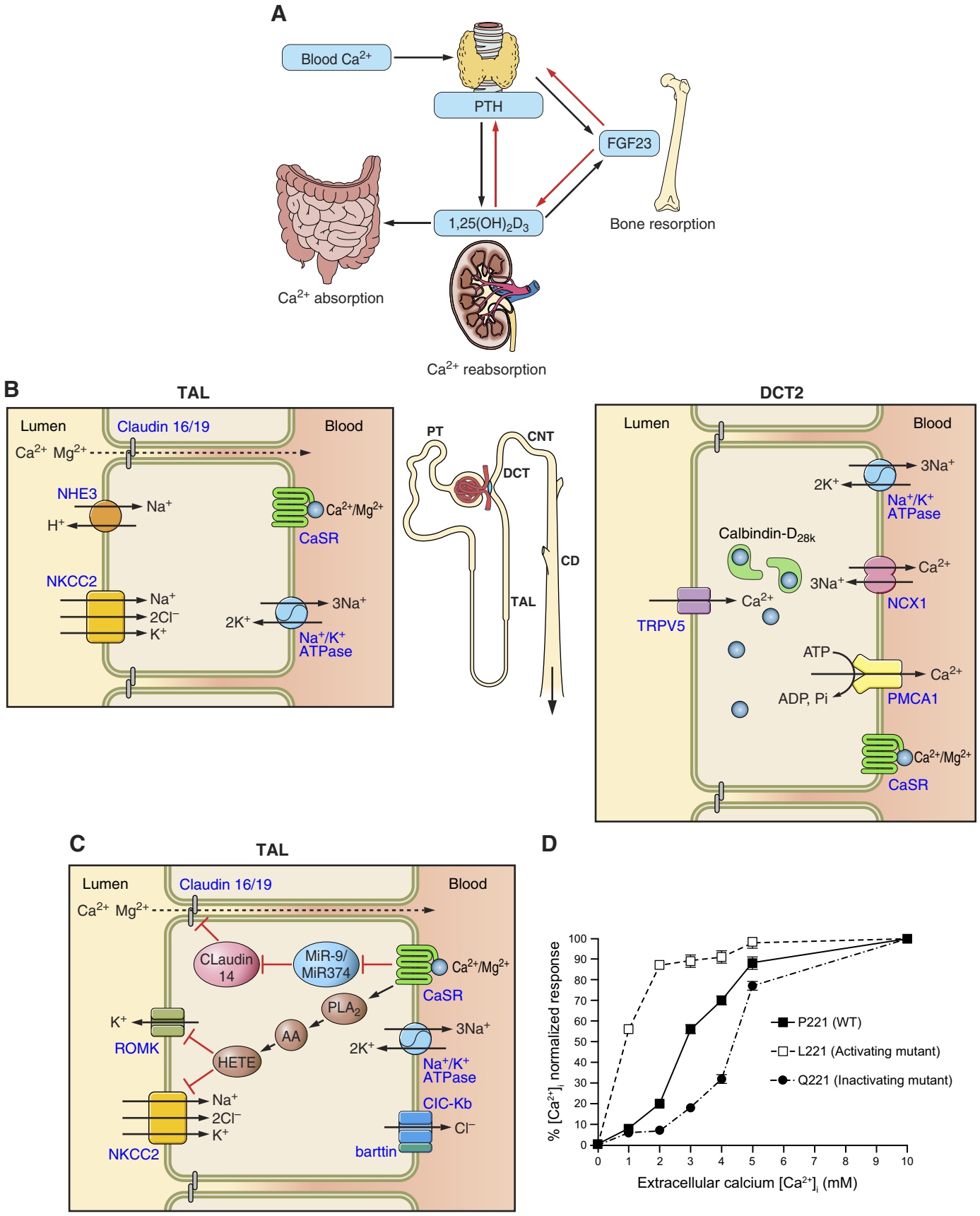
Within the kidney, glomerular filtration of Ca^{2+} includes its ionized form and Ca^{2+} complexed to small anions. The Ca^{2+} ions bound to plasma proteins are not filtered. Subsequently, the majority of the filtered Ca^{2+} is reabsorbed via passive paracellular transport in the PT that is mainly diffusive and in part facilitated by solvent drag. This is mainly influenced by Na^+ availability and Na^+ backleak. In addition, the paracellular transport of Ca^{2+} (and Mg^{2+} in more distal segments, see later) occurs via specialized tight junction proteins, the claudins. Claudins consist of four transmembrane helices, intracellular NH_2- and COOH-tails, and two extracellular loops that play a role in ion selectivity and interaction with the claudins of adjacent cells (721). Claudins usually associate into dimers or oligomers that involve either homo- or heteromeric interactions (223), which can form antiparallel double rows (722). The composition of tight junctions with different claudin members determines the characteristic properties regarding the paracellular permeability and/or transepithelial resistance in specific epithelia (250, 273). In the proximal tubule, the pore-forming claudins 2, 10a, 11, and 17 have been reported to be involved in paracellular Ca^{2+} transport (385, 409; for extensive review, see Ref. 314). Furthermore, microperfusion studies have suggested the presence of active Ca^{2+} transport in the pars recta of the PT, but the protein(s) responsible for this transport remain(s) to be identified (627).

Next, Ca^{2+} reabsorption takes place in the TAL and proceeds through the paracellular pathway driven by the positive transepithelial voltage that is established by the NKCC2-mediated Na^+ reabsorption and subsequent K^+ secretion via ROMK. The permeability for Ca^{2+} (and Mg^{2+}) is determined by specific tight junction proteins, claudin-16 and claudin-19. Recently, claudin-14 has been identified as inhibitor of the claudin-16/19 complex (251). Finally, a small portion (10–15%) of filtered Ca^{2+} is actively reabsorbed in the DCT2 and the CNT through a so-called three-step process. First, Ca^{2+} enters the cell via the epithelial Ca^{2+} channel TRPV5. Then Ca^{2+} is bound to calbindin-D_{28K} and diffuses to the basolateral side, where the extrusion process is mediated via the Na^+-Ca^{2+}-exchanger (NCX1) and the plasma membrane Ca^{2+}-ATPase PMCA1b (303) **(FIGURE 12)**.

An additional player is the CaSR that responds to changes in ionized plasma Ca^{2+}. As aforementioned, the CaSR regulates PTH release that stimulates Ca^{2+} mobilization from bone and leads to increased Ca^{2+} reabsorption via $1,25(OH)_2D_3$. Furthermore, the CaSR is expressed in the kidney where it participates in the Ca^{2+} homeostasis via a PTH-independent pathway (445). The underlying mechanism mainly involves an increase in Ca^{2+} reabsorption in the TAL, which has recently been shown to implicate regulation of claudin-14 expression via the calcineurin-NFATc1-microRNA pathway (248, 251). An additional mechanism evoked by the CaSR in the TAL involves phospholipase A_2 (PLA_2) activation and a subsequent increase in cytosolic arachidonic acid, which is then metabolized to 20-hydroxyeicosatetraenoic acid (20-HETE) (795). Both mechanisms will be discussed in more detail below, since abnormalities of the CaSR signaling are associated with hypercalcemic and hypocalcemic disorders.

2. Familial hypocalciuric hypercalcemia

A) BRIEF CLINICAL DESCRIPTION. Familial hypocalciuric hypercalcemia (FHH) (MIM no. 145980), initially referred to as familial benign hypercalcemia, is an autosomal dominant disorder that was first characterized in 1972 (214). Patients usually display a mild hypercalcemia, together with inappropriately low urinary Ca^{2+} excretion (214, 461, 552). The disease is often made after fortuitous discovery of hypercalcemia. As a result of hypercalcemia, patients may develop chondrocalcinosis and vascular calcification with age (291). Further biochemical characteristics consist of mild hypermagnesemia and normal to slightly elevated levels of serum PTH (291). FHH is usually asymptomatic, but fatigue, weakness, and excessive thirst may be experienced. Most of the time, treatment is not necessary. Yet, the calcimimetic (i.e., activator of the calcium-sensing receptor, see



below) cinacalcet appears to be an effective treatment in symptomatic FHH patients (472). Pregnant women with FHH must be monitored as an elevated hypercalcemia may inhibit PTH secretion in the developing fetus, which is then prone to developing severe hypocalcemia directly after birth (329). Importantly, Ca^{2+} levels should be monitored in newborns of two FHH parents as they can present the severe recessive disorder neonatal severe hyperparathyroidism (see below).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. FHH is a genetically heterogeneous disorder with three variants: types 1, 2, and 3. FHH type 1 (MIM no. 145980) is due to loss-of-function mutations in the *CASR* gene, coding for the CaSR (572). The CaSR is a guanine nucleotide-binding protein (G protein)-coupled receptor that signals through the G protein subunit α_{11} ($G\alpha_{11}$). FHH type 2 (MIM no. 145981) is due to mutations in *GNA11* (512), resulting in $G\alpha_{11}$ loss of function. Vice versa, *GNA11* mutations leading to $G\alpha_{11}$ gain of function, like *CaSR* mutations affecting CaSR gain of function that cause autosomal dominant hypocalcemia type 1, lead to hypocalcemia (282). FHH type 3 (MIM no. 600740) is associated with *AP2S1 (*adaptor-related protein complex 2, sigma 1 subunit) mutations that lead to altered CaSR endocytosis (283, 513).

The majority of FHH cases investigated to date are associated with loss-of-function mutations in the *CASR* (CaSR Database: http://www.casrdb.mcgill.ca/). In 1993, Brown et al. (82) cloned the CaSR from bovine parathyroid gland and demonstrated that it belongs to the G protein-coupled receptor family and responds to changes in extracellular Ca^{2+} (and Mg^{2+}). Subsequent cloning and characterization of the human CaSR revealed that it functions as a glycolysated dimer (233, 569). The receptor consists of a large extracellular NH_2-terminal domain, seven transmembrane spanning regions, and a long intracellular COOH terminus. Ligand binding at the extracellular domain activates either the G_q-, G_i-linked signaling, which in turn stimulates a variety of cell signaling pathways including the mitogen-activated protein kinases (MAPKs), PLA_2, phospholipase D, phosphatidylinositol 3-kinase (PI3K, leading to activation of the Akt pathway), and phospholipase C that increases the inositol 1,4,5-trisphosphate (IP_3)-dependent intracellular Ca^{2+} release (305).

Most missense mutations in *CASR* cluster within the extracellular domain of the CaSR that has a proposed role in Ca^{2+} sensing and binding (284, 323). Indeed, expression studies have demonstrated a right shift in the dose-response curve of mutant CaSR proteins compared with the wild-type, meaning a decrease in sensitivity towards the extracellular Ca^{2+} concentration (284, 558) **(FIGURE 12)**. Other mutations are localized in the transmembrane segments, which could inhibit the transmission of activation signals to the intracellular signaling pathways (320, 415). Additional missense mutations lead to impaired trafficking to the plasma membrane as a result of incorrect processing at either the ER or Golgi apparatus (324, 809). Interestingly, there seems to be a genotype-phenotype correlation in which the dominant-negative effect of missense mutations on wild-type CaSR function leads to a more severe phenotype than observed in patients harboring heterozygous truncating mutations (526, 797). It should be noted that common variants in the *CASR* gene have been consistently associated with serum Ca^{2+} levels in GWAS studies involving populations of European, Indian and Asian descent (371, 533, 776).

The CaSR mainly exerts its function in tissues directly related to Ca^{2+} homeostasis as it is highly expressed in the parathyroid gland and the kidney, but it can also be found in bone, colon, thyroid gland, brain, and pancreas (606). In the parathyroid gland, it regulates the secretion of PTH that can indirectly [via $1,25(OH)_2D_3$ production in the kidney] control intestinal Ca^{2+} absorption, Ca^{2+} release from bone, and also Ca^{2+} reabsorption in the kidney. PTH secretion is suppressed upon stimulation of the CaSR by high extracellular ionized Ca^{2+} concentrations, while low Ca^{2+} concen-

FIGURE 12. Calcium homeostasis. *A*: Ca^{2+} homeostasis is maintained through the coordinated actions of intestinal absorption, storage in bone, and urinary excretion by the kidney. Changes in serum Ca^{2+} are sensed by the parathyroid gland that can release PTH. The PTH-$1,25(OH)_2D_3$-FGF23 axis is an essential hormonal control mechanism that coordinates the Ca^{2+} balance. In short, release of PTH can stimulate bone resorption, renal Ca^{2+} reabsorption, and renal production of active vitamin D [$1,25(OH)_2D_3$] to increase intestinal Ca^{2+} absorption. Additionally, $1,25(OH)_2D_3$ stimulates FGF23 production in bone, which acts as a negative feedback loop to inhibit PTH and $1,25(OH)_2D_3$ production. The arrows indicate the direction of the pathway; red denotes inhibitory actions, and black depicts stimulatory actions. *B*: reabsorption of Ca^{2+} in the kidney occurs through a paracellular pathway in the PT and TAL, the latter involving the claudins 16/19. Fine-tuning of the final Ca^{2+} excretion occurs in the DCT via transcellular transport. Here, Ca^{2+} is reabsorbed at the apical membrane through TRPV5, is subsequently bound to calbindin-D_{28k}, and is transported to the basolateral where it is extruded via the Ca^{2+} pump PMCA and the NCX1 Ca^{2+} exchanger. *C*: activation of the CaSR at the basolateral membrane of the TAL inhibits the process of NaCl reabsorption via blocking NKCC2 and ROMK. This occurs via activation of HETE that is metabolized from AA, which in turn is produced by PLA_2. Furthermore, activation of the CaSR acts on the clauding16/19-mediated paracellular transport via inhibition of microRNA-claudin-14 pathway. *D*: functional analysis of the Ca^{2+} response, evoked by extracellular Ca^{2+} changes, of wild-type and various CaSR mutants in transfected HEK293 cells. The depicted CaSR mutants showed a leftward (activating mutant) and a rightward (inactivating mutant) shift in the concentration-response curve compared with the wild-type (wt) CaSR. AA, arachidonic acid; CaSR, calcium sensing receptor; DCT, distal convoluted tubule; FGF23, fibroblast growth factor 23; HETE, 20-hydroxyeicosatetraeonic acid; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PLA_2, phospholipase A_2; PMCA, plasma membrane calcium ATPase; PT, proximal tubule; PTH, parathyroid hormone; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb of Henle's loop; TRPV5, transient receptor potential vanilloid type 5. [Adapted from Hannan et al. (284), with permission from Oxford University Press.]

trations result in the synthesis and secretion of PTH (488, 504, 511). The expression of the CaSR in the kidney has been widely studied, with the first studies showing a nephron-wide distribution with distinct cellular polarization per segment, but most significant abundance at the basolateral membrane in the TAL (445, 604, 605) **(FIGURE 12)**. The CaSR regulates the urinary Ca^{2+} excretion, and its mechanisms of action will be discussed in more detail in the forthcoming paragraphs. Overall, the inactivating *CaSR* mutations in FHH "reset" the Ca^{2+}-dependent setpoint for PTH release to a higher than normal plasma Ca^{2+} concentration, thereby explaining the inappropriate control of Ca^{2+} homeostasis and resulting hypercalcemia. In addition, defective CaSR in the kidney leads to increased tubular Ca^{2+} reabsorption. The renal Ca^{2+} handling in FHH seems independent of PTH, as parathyroidectomy did not improve the hypocalciuria (141, 463). Often, patients are treated with the loop diuretic ethacrynic acid that increases the urinary Ca^{2+} excretion. This occurs via inhibition of NKCC2 in the TAL, which in turn suppresses the passive Ca^{2+} reabsorption, suggesting that FHH patients have an abnormal TAL function (25).

The FHH type 2-causing mutations are located within the GTPase domain of the $G\alpha_{11}$-subunit, which are predicted to diminish CaSR signal transduction by influencing the interaction of $G\alpha_{11}$ with downstream effectors (282). Mutations in *AP2S1*, related to FHH type 3, were shown to disrupt the AP2 complex, which is a central component of clathrin-coated vesicles that facilitate endocytosis of plasma membrane proteins. The loss of interaction between the AP2 complex and the COOH terminus of the CaSR leads to impaired endocytosis and thus disrupts signal transduction in a dominant-negative manner (282).

3. Neonatal severe hyperparathyroidism

A) BRIEF CLINICAL DESCRIPTION. In contrast to FHH, the autosomal recessive disorder neonatal severe hyperparathyroidism (NSHPT) (MIM no. 239200) is a potentially life-threatening condition that is characterized by severe neonatal hypercalcemia and highly elevated serum PTH levels. Other phenotypic features include failure to thrive, markedly enlarged parathyroid glands, and undermineralization of bone resulting in bone abnormalities, multiple fractures, and ribcage deformities that may lead to respiratory problems (235, 299). The severe hypercalcemia and hyperparathyroidism associated with NSHPT are challenging and require specific measures. The acute management of hypercalcemia classically relies on saline perfusion and use of loop diuretics. Pamidronate, a biphosphonate drug that could halt the bone resorption process mediated by uncontrolled hyperparathyroidism, has been successfully used in NSHPT patients to control severe hypercalcemia before parathyroidectomy (790). Radical subtotal parathyroidectomy is often the treatment of choice in NSHPT (96). In addition, calcimimetic CaSR activators may be of interest in NSHPT (232). The disorder was originally described before the identification of FHH (235, 299), but later discovered to develop in children from consanguineous parents with FHH (462, 707). In line with this, *CaSR* mutations are shown to be the causative factor.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Pollak et al. (572) identified several homozygous and compound heterozygous mutations in the *CASR* gene in patients with NSHPT. To study the role of CaSR, various mouse models have been investigated over the past years. Mice heterozygous for the *Casr* gene mimic the FHH phenotype, while *Casr* KO mice exhibited a phenotype resembling NSHPT (302). These *Casr*-null mice have severe hyperparathyroidism and hypercalcemia, as well as bone abnormalities and growth retardation, and they die within a few days after birth. This lethality can be rescued by genetic ablation of *Pth* since double KO (*Pth* and *Casr*) mice have normal development compared with control littermates (402). Importantly, the serum Ca^{2+} levels and renal Ca^{2+} excretion remained affected, indicating that the CaSR has an additional role in renal Ca^{2+} handling independent of PTH (370, 402). Later studies found that targeting exon 5 of the *Casr* produced a truncated CaSR due to alternative splicing; this CaSR isoform is able to partly compensate for the loss of the CaSR in some tissues (536, 619). Additional mouse models have been generated that allowed inducible tissue-specific deficiency of the CaSR (104, 746). Toka et al. (746) studied kidney-specific *Casr* KO mice and found that serum levels of Ca^{2+}, Mg^{2+}, and PTH were unaltered compared with control mice. However, these mice display significantly diminished Ca^{2+} excretion when fed a high-Ca^{2+} diet. Furthermore, a marked downregulation of claudin-14, modest upregulation of claudin-16, and increased NKCC2 activity were observed (746). Claudin-16 can interact with claudin-19 to form a paracellular complex that regulates cation reabsorption in the TAL (315). Recently, claudin-14 was shown to control renal Ca^{2+} handling via negative regulation of the claudin-16/19 complex (249, 251). Together with its expression in the basolateral membrane of TAL cells (604, 605), it suggests that the CaSR plays a role in regulating paracellular Ca^{2+} transport in this segment.

The latter notion is supported by an in vitro study demonstrating that CaSR activation in MDCK cells results in deposition of tight junction components at the cell membrane, influencing the transepithelial electrical resistance (358). Another study used *Cldn14*-deficient mice and transgenic animals overexpressing claudin-14 to show that the CaSR alters the tight junction permeability via the calcineurin-NFATc1-microRNA-claudin-14 pathway (249) **(FIGURE 12)**. These investigators demonstrated that the *Cldn14* gene transcription is controlled by the microRNAs miR-9 and miR-374, which in turn are reg-

ulated by promoter binding of nuclear factor of activated T cell (NFAT) induced by CaSR signaling in the kidney (249, 251). This mechanism was substantiated by Gong et al. (248) demonstrating that the transcription of renal miR-9 and miR-374 can be stimulated by treatment with histone deacetylase (HDAC) inhibitors. This will downregulate claudin-14, thereby relieving its repression on paracellular transport and resulting in reduced urinary Ca^{2+} excretion in treated mice (248). In short, the targeted deletion of CaSR in mice has provided attractive models of the human syndromes and proved to be helpful in unraveling the role of the CaSR in the kidney. Furthermore, parathyroidectomized rats were shown to develop hypocalciuria and hypercalcemia despite PTH supplementation (445), thereby confirming a PTH-independent role of the CaSR in the regulation of the Ca^{2+} balance.

4. Autosomal dominant hypocalcemia

A) BRIEF CLINICAL DESCRIPTION. In contrast to the loss-of-function mutations that lead to hypercalcemic disorders, gain-of-function mutations in the *CASR* gene are associated with hypocalcemic defects. Autosomal dominant hypocalcemia (ADH) (MIM no. 601198), also referred to as autosomal dominant hypocalcemic hypercalciuria, is generally characterized by a mild asymptomatic hypocalcemia, together with renal Ca^{2+} wasting (559, 573). The phenotype and age of onset depend on the degree of hypocalcemia and are particularly variable, ranging from asymptomatic individuals to patients with rather mild symptoms (cramps, weakness, paresthesia) and patients with severe symptoms that include recurrent seizures, nephrocalcinosis, and impaired renal function. Neonatal seizures and carpo-pedal spasm have been reported in a few cases (559). Other biochemical features comprise hyperphosphatemia and hypomagnesemia, which are also observed in related diseases like hypoparathyroidism and pseudohypoparathyroidism that arise from tissue resistance to PTH (35, 209, 562). Appropriate diagnosis is important to avoid vitamin D analog treatment in ADH, as it worsens the hypercalciuria and may lead to complications such as nephrocalcinosis, nephrolithiasis, and renal failure (559). Instead, hypocalciuric compounds including PTH and thiazides are generally used, as well as calcilytics (CaSR antagonists) (425, 489, 647). Careful monitoring of urinary Ca^{2+} levels and regular kidney ultrasound are essential for the maintenance of Ca^{2+} homeostasis and treating the clinical signs of hypocalcemia.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Activating mutations of the *CASR* gene were first described in families affected with ADH (558, 573). These are most often missense mutations occurring in the extracellular NH_2-terminal domain and in the outer loops of the signal transduction domain of the CaSR (568). They may alter receptor conformation and were shown to cause a leftward shift in the dose-response curve towards the extracellular Ca^{2+} concentration (558, 573). In addition to this increased Ca^{2+} sensitivity, a large deletion of the intracellular COOH terminus was found to increase the cell surface expression of the CaSR (432). Gain-of-function mutations in *GNA11*, which encodes $G\alpha_{11}$ that mediates the signaling of the CaSR, were also recently reported in association with ADH (512). The altered CaSR activity results in inappropriately low serum PTH and decreased reabsorption of Ca^{2+} in the TAL, leading to Ca^{2+} wasting. The impaired reabsorption of Ca^{2+} in the TAL is thought to be due to a reduction of the paracellular permeability and/or to a decreased lumen-positive transepithelial voltage as a result of defective transcellular NaCl reabsorption (83).

Next to the typical mild form of ADH, some severe mutations have been identified in patients suffering from symptomatic hypocalcemia together with a Bartter-like syndrome that involves hypokalemic metabolic alkalosis, elevated plasma renin, and hyperaldosteronism (770, 800). This condition was previously known as Bartter syndrome type 5; functional analysis of these *CASR* mutations has demonstrated even higher affinity for extracellular Ca^{2+} than those observed for mutant receptors associated with ADH alone (319, 770, 800). These observations suggest that the additional features that occur in Bartter syndrome type 5 are due to severe gain of CaSR function (557). In a physiological setting, CaSR activation in TAL stimulates intracellular Ca^{2+} signaling that modulates PLA_2 activity, which in turn increases cytosolic arachidonic acid that is rapidly metabolized to 20-HETE or to prostaglandins (798). These signaling pathways have been linked to inhibition of NKCC2 and ROMK (9, 792, 793, 795). This means that enhanced activity of CaSR in TAL disturbs NaCl reabsorption directly mediated by NKCC2 and indirectly via ROMK channels, as K^+ recycling contributes to the NKCC2 transport rate. Furthermore, inhibition of ROMK and NKCC2 will lower the lumen-positive transepithelial voltage, which then diminishes paracellular Ca^{2+} and Mg^{2+} transport, resulting in TAL dysfunction resembling Bartter syndrome **(FIGURE 12)**.

A point of attention is that the intracellular signaling pathways activated by the CaSR are also stimulated by other receptor signaling involving angiotensin II and endothelin, which are not known to cause renal NaCl or K^+ wasting. This indicates that the CaSR functions via additional mechanisms, which could imply regulation of transporters in other nephron segments. There is some evidence of apical CaSR expression in the PT regulating the PTH-mediated phosphate excretion (28). A recent study suggested a new role of the CaSR in modulating fluid reabsorption as well as H^+ secretion in the PT, via stimulation of NHE3 (95). Activating the CaSR increased NHE3 activity leading to enhanced Na^+ reabsorption, which drives fluid reabsorption.

The concomitant H^+ secretion is thought to result in ionization of Ca^{2+}, which prevents its precipitation in the distal parts of the nephron (95). Thereby, CaSR activation would drive both fluid reabsorption in the PT and Ca^{2+} reabsorption in the distal nephron. Expression of the CaSR has also been reported on the apical and basolateral membranes of the DCT and CNT (604, 747), but its physiological role there remains to be established. Available evidence suggests the CaSR controls apical Ca^{2+} influx through TRPV5 and/or basolateral exit via NCX and PMCA in the DCT2/CNT (170, 747). An interaction of the CaSR with the inwardly rectifying K^+ channel Kir4.1, expressed at the basolateral membrane of the DCT, has also been demonstrated (100, 322). The CaSR was shown to block Kir4.1 channel activity by reducing its expression at the plasma membrane (100). Within the collecting duct, the CaSR is present in both principal and intercalated cells (604), where it is proposed to play a role in diuresis to prevent kidney stone formation upon hypercalciuria (581, 601, 636). The latest study suggests that activation of the CaSR leads to a reduced vasopressin response for aquaporin2 (AQP2) translocation, and subsequently reduces water reabsorption, functioning as a defense mechanism against kidney stones (581). This is in agreement with an earlier finding that mice deficient of *Trpv5* do not develop kidney stones despite the strong hypercalciuria (304). Instead, the *Trpv5*$^{-/-}$ mice have an enhanced urinary acidification and polyuria, likely due to the effects of the CaSR on the H^+-ATPase activity and AQP2 expression (601).

Together, these data suggest that the role of the CaSR in the kidney is not restricted to Ca^{2+} handling. Based on its basolateral expression in TAL and DCT, it may sense plasma Ca^{2+} levels in these segments and function as modulator of Ca^{2+} reabsorption by affecting either the passive or active transport pathways. In addition, the CaSR has antiphosphaturic effects in PT that might counteract possible Ca^{2+}-phosphate precipitation in distal tubular segments. Furthermore, it promotes acidification and polyuria through its action in the CD. Hence, the CaSR seems to have established an integrated system, regulating various levels of fluid and electrolyte management, to prevent nephrocalcinosis and kidney stone formation. Developing CaSR modulators with some specificity for the kidney could allow modulation of renal actions and function as therapeutics of the Ca^{2+}-related diseases.

F. Disorders of Magnesium Transport

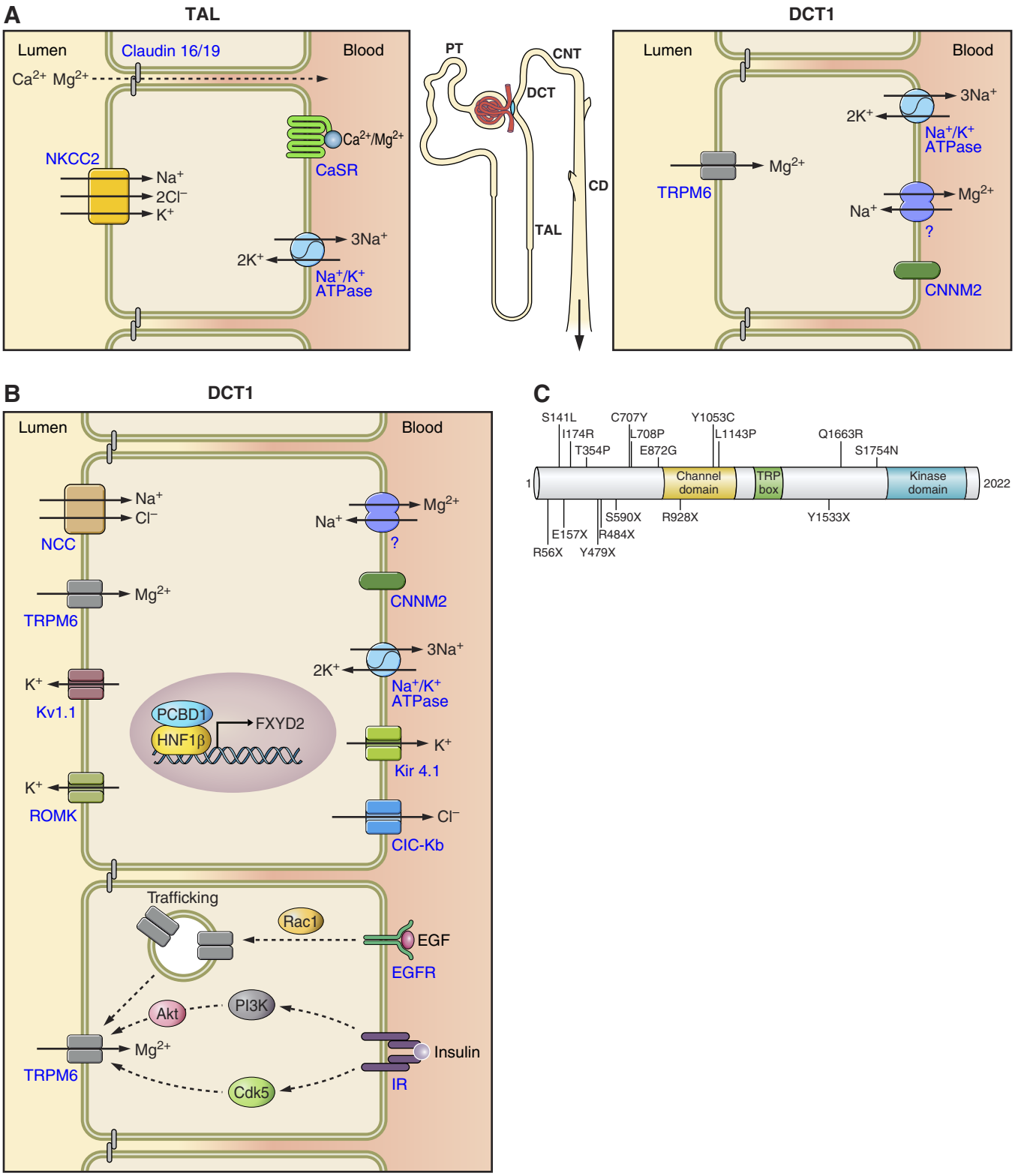
1. Renal magnesium handling

Mg^{2+} is an essential divalent cation that participates in a wide spectrum of processes involving intracellular signaling, neuromuscular excitability, bone formation, and enzyme activation (186, 212). The maintenance of the Mg^{2+} balance is crucial for many physiological functions, and plasma Mg^{2+} concentrations are kept within a defined range (0.7–1.1 mM) via (re)absorption in the intestine and kidney, and exchange with the bone. The skeleton functions as a major Mg^{2+} store, resulting in only 1% of the total body Mg^{2+} as the circulating plasma Mg^{2+} (789). Ultimately, these Mg^{2+} levels are defined by the final urinary Mg^{2+} excretion, which is tightly regulated by the kidney (174, 587). Here, the majority of filtered Mg^{2+} is reabsorbed in the PT (15–20%) and TAL (65–70%) via passive paracellular transport. Similar to Ca^{2+} transport, the claudin-16/19 complex is responsible for Mg^{2+} reabsorption in the TAL, which is driven by the positive transepithelial voltage. Several hormones, including PTH, glucagon, calcitonin, and insulin, were shown to stimulate Mg^{2+} reabsorption in this segment, either via influencing the transepithelial voltage by affecting NKCC2 transport or ROMK activity or by modifying the paracellular permeability through the claudins (168, 588). Similarly, activation of the CaSR in the TAL can inhibit paracellular Mg^{2+} transport (293). Furthermore, a number of other electrolyte disturbances like metabolic acidosis, K^+ depletion, and hypophosphatemia also affect renal Mg^{2+} transport by changing the transepithelial voltage or the permeability of the paracellular pathway. Final regulation of the urinary Mg^{2+} excretion takes place in DCT1 where the remaining 10% of filtered Mg^{2+} is reabsorbed by an active transcellular mechanism (140). Here, Mg^{2+} enters the cell via the epithelial Mg^{2+} channel TRPM6, dependent on the negative apical transmembrane potential. This is established by apical K^+ secretion via the K^+ channels Kv1.1 and/or ROMK (717). Furthermore, Mg^{2+} transport via TRPM6 can be stimulated by a number of hormones including epidermal growth factor (EGF), insulin, and estrogen (265, 266, 508). The mechanism of Mg^{2+} extrusion at the basolateral membrane is still not understood, but likely comprises a Na^+-dependent transporter. In addition, two other basolateral proteins, the K^+ channel Kir4.1 and γ-subunit of Na^+-K^+-ATPase, are identified as important factors in generating a Na^+ gradient that drives Mg^{2+} reabsorption in DCT1 (62, 477) **(FIGURE 13)**.

Disturbances in the Mg^{2+} balance are often secondary to diseases like diabetes mellitus, osteoporosis, asthma, and heart and vascular disease, or Mg^{2+} depletion occurs upon treatment with various drugs including loop diuretics, thiazides, immunosuppressants, anticancer drugs, proton pump inhibitors. Studies of inherited forms of hypomagnesemia and experimental findings of several animal models have greatly increased our knowledge of renal Mg^{2+} reabsorption mechanisms. Identification of the affected nephron segments, different modes of inheritance, and additional characteristic symptoms has helped in the classification of the Mg^{2+} wasting disorders, which is discussed in more detail in the forthcoming paragraphs.

2. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

A) BRIEF CLINICAL DESCRIPTION. In 1975, a case report described the phenotype of a young man with hypomagnesemia and accompanying renal Mg^{2+} and Ca^{2+} wasting, that also exhibited progressive nephrocalcinosis and chondrocalcinosis (630). Subsequent studies enabled full characterization of the disorder named as familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC, also named



hypomagnesemia 3, HOMG3; MIM no. 248250) (517, 577, 620). The patients present in childhood with polyuria-polydipsia, urinary tract infections, and kidney stones, and extrarenal manifestations such as failure to thrive, tetany, seizures, and nystagmus have also been reported (517, 620). Additional biochemical characteristics include elevated PTH levels, incomplete distal tubular acidosis, hypocitraturia, and hyperuricemia in most patients. In addition to the classical FHHNC phenotype, a subset of patients was identified with severe ocular abnormalities. This appeared to be associated with a different genetic defect and was therefore termed FHHNC with severe ocular involvement (also named hypomagnesemia 5, HOMG5; MIM no. 248190) (399). Due to the hypercalciuria and nephrocalcinosis, patients often progress to chronic kidney disease within the first two decades of life, and a significant number of patients develop end-stage renal disease later in life. Initial therapy aims at restoring the plasma Mg^{2+} levels and reducing the hypercalciuria by chronic Mg^{2+} supplementation and thiazide treatment, respectively. However, this treatment is in general insufficient to prevent the progression of nephrocalcinosis and stone formation (577, 753, 801).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. By using a positional cloning approach, Simon et al. (693) found mutations in *CLDN16*, the gene encoding the tight junction protein claudin-16 (initially named paracellin-1) as associated with FHHNC/HOMG3. Claudin-16 is expressed in the TAL and plays a role in paracellular cation permeability (385, 693). Most reported *CLDN16* mutations are missense mutations that target either the transmembrane domains or the extracellular loops, with a clustering in the first extracellular loop that is important for ion selectivity. Within this domain, patients originating from Germany or Eastern European countries exhibit a common *CLDN16* mutation (L151F) due to a founder effect (801). As this mutation is present in ~50% of mutant alleles, molecular diagnosis is greatly facilitated in patients originating from these countries. A few years later, mutations were also identified in the *CLDN19* gene, coding for claudin-19, associated with HOMG5 (399). Claudin-19 colocalizes with claudin-16 in the kidney, but it is also highly expressed in the retina explaining the severe ocular problems observed in patients with *CLDN19* mutations (399). A cohort study presented a genotype-phenotype correlation demonstrating that FHHNC patients with *CLDN16* mutations leading to a complete loss-of-function on both alleles display a younger age onset as well as a more rapid decline in renal function compared with patients with residual claudin-16 function (398). On the other hand, phenotypical variability is even found in families with members having the same homozygous *CLDN16* or *CLDN19* mutation (20, 670).

The claudin-16 and -19 isoforms are both highly enriched in the TAL. Hou et al. (315) demonstrated that claudin-16 and claudin-19 interact to form a cation-selective pore. Overexpression studies showed that several FHHNC mutations in *CLDN16* and *CLDN19* disrupt this interaction and abolish the cation selectivity of the encoded claudins (316). However, other studies have shown conflicting results on the claudin-16/19 permeability properties, and the direct effects on Mg^{2+}/Ca^{2+} permeation do not fully explain the strong hypercalciuria and hypermagnesiuria observed in FHHNC patients (313, 337, 374). The idea is that the mutant claudin proteins impair the electrical driving force necessary for passive transport. Overexpression of claudin-16 significantly increased the Na^+ permeability (P_{Na}), which was not observed for the FHHNC disease mutants of claudin-16 (313). Furthermore, ex vivo perfusion measurements of TAL segments from *Cldn16* knockdown (KD) mice demonstrated that the ion permeability ratio for Na^+ over Cl^- (P_{Na}/P_{Cl}) was decreased (317). On the other hand, overexpression of claudin-19 led to a decrease in Cl^- permeability, meaning that coexpression with claudin-16 results in a large increase in P_{Na}/P_{Cl} that ultimately generates the transepithelial voltage (316, 680). Hence, loss-of-function mutations in *CLDN16* and *CLDN19* would abrogate this electrical driving force for paracellular Ca^{2+} and Mg^{2+} reabsorption in TAL.

The latter hypothesis has been supported by studies in mouse models. Hou et al. (317) used RNA interference to

FIGURE 13. Magnesium transport in the kidney. *A*: the major amount of filtered Mg^{2+} is reabsorbed through a paracellular route in the PT and TAL. Here, claudin-16 and claudin-19 constitute the paracellular Mg^{2+} pathway. The final reabsorption of Mg^{2+} takes place in the DCT via the apical Mg^{2+} channel TRPM6. *B*: Mg^{2+} reabsorption in DCT is mediated by TRPM6. Here, transport of Mg^{2+} is primarily driven by the electrical gradient over the apical membrane, which is established by the voltage-gated K^+ channels Kv1.1 and ROMK. Moreover, the hormones EGF and insulin are involved in the membrane expression of TRPM6 through intracellular signaling involving Cdk5, PI3K, Akt, and Rac1. Extrusion of Mg^{2+} at the basolateral membrane occurs via a yet unknown mechanism, possibly regulated by CNNM2 functioning as a Mg^{2+} sensor. The Na^+-K^+-ATPase generates the electrochemical gradient essential for the transport processes, and its activity is dependent on K^+ recycling via Kir4.1 at the basolateral membrane. Furthermore, FXYD2 is known as a regulatory subunit of the Na^+-K^+-ATPase, and its transcription is regulated by HNF1β and the cofactor PCBD1. *C*: schematic representation of the domain structure of TRPM6 depicting the missense mutations identified in patients suffering from hypomagnesemia with secondary hypocalcemia. Akt, protein kinase B; Cdk5, cyclin-dependent kinase 5; ClC-Kb, chloride channel Kb; CNNM2, cyclin M2; DCT, distal convoluted tubule; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FXYD2, FXYD-domain containing ion transport regulator 2; HNF1β, hepatocyte nuclear factor-1β; IR, insulin receptor; Kir4.1, inwardly rectifying K^+ channel; Kv1.1, voltage-gated K^+ channel 1.1; NCC, Na^+-Cl^- cotransporter; PCBD1, pterin-4 alpha-carbinolamine dehydratase 1; PI3K, phosphoinositide 3-kinase; PT, proximal tubule; Rac1, Ras-related C3 botulinum toxin substrate 1; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb of Henle's loop; TRPM6, transient receptor potential melastatin type 6.

generate *Cldn16*-deficient mice that had >99% knockdown (KD) of claudin-16 expression in the kidneys. These mice show typical FHHCN symptoms including hypomagnesemia, high urinary excretion of Ca^{2+} and Mg^{2+}, and nephrocalcinosis (317). Similarly, *Cldn19* KD mice exhibit low serum Mg^{2+} together with urinary Ca^{2+} and Mg^{2+} wasting (315). While the KD models favor a reduction in Na^+ selectivity as causative factor of renal wasting in FHHNC, a study on *Cldn16* KO mice demonstrated reduced Mg^{2+} and Ca^{2+} permeability in microperfused TAL segments (810). A third isoform enriched in the TAL, claudin-14, may interact with claudin-16, causing the inhibition of the claudin-16/19 complex. As described in section III*E3*, the expression of claudin-14 is positively regulated by the CaSR via a microRNA-dependent mechanism (251). Genome-wide association studies support the relevance of this mechanism, since common variants in *CLDN14* are associated with increased risk of kidney stones and the urinary Mg^{2+} to Ca^{2+} ratio in the general population (134).

The importance of claudins in electrolyte balance was further emphasized by the recent identification of mutations in *CLDN10*, encoding claudin-10, by three independent groups (65, 277, 386). Claudin-10 has two major isoforms that can form paracellular channels with different ion selectivity (767). Mutations in either of the isoforms were associated with an autosomal recessive disorder that is characterized by hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia (HELIX syndrome; MIM no. 617671). The patients had renal salt wasting, with hyperaldosteronism and hypokalemia, and mild Ca^{2+} and Mg^{2+} retention. Interestingly, the biochemical characteristics were in line with findings in the tubule-specific *Cldn10* KO mice (79). Functional analysis in isolated perfused TAL tubules of these mice demonstrated a decreased paracellular Na^+ permeability and a relatively increased permeability of Ca^{2+} and Mg^{2+} (79). Of note, claudin-10 shows a higher expression in the inner stripe of the outer medulla (ISOM), whereas claudin-16 and claudin-19 predominate in the outer stripe (OSOM) and the cortex. Furthermore, the channels formed by claudin-10b are selectively permeable for Na^+, whereas claudin-16 and -19 are permeable for Mg^{2+} and Ca^{2+} (485). These data, recently supported by studies using double KO mice for *Cldn16* and *Cldn10* (78), support the existence of a longitudinal specialization of paracellular transport within the TAL segment **(FIGURE 14)**. In addition to the paracellular reabsorption of Ca^{2+} and Mg^{2+} (in the OSOM and cortex) via the claudin-16/19 complex, the lumen-positive transepithelial potential drives the paracellular reabsorption of Na^+ (in the ISOM) via claudin-10b. Recently, Miltaz et al. (485) hypothesized that the high paracellular and transcellular Na^+ reabsorption without water in the ISOM leads to a hyposmotic luminal fluid in the cortical TAL, resulting in Na^+ diffusion from interstitium to lumen (via claudin-10b) along its concentration gradient, via the paracellular pathway created by claudin-10b. In turn, this Na^+ diffusion contributes to the lumen-positive potential as a driving force for Ca^{2+} and Mg^{2+} reabsorption (544). Together, these studies support further understanding of tight junction formation and provide essential information on the selectivity of the pore region.

3. Isolated dominant renal hypomagnesemia

A) BRIEF CLINICAL DESCRIPTION. Nearly three decades ago, two initially unrelated Dutch families were reported with dominant renal hypomagnesemia associated with hypocalciuria (IDH, also named hypomagnesemia 2, HOMG2; MIM no. 154020) (239). They had increased urinary Mg^{2+} values, showed lowered urinary Ca^{2+} excretion, and suffered from generalized convulsions, cramps, and chondrocalcinosis. The serum Mg^{2+} levels were <0.4 mM, without other plasma electrolyte abnormalities. A ^{28}Mg-retention study in one of the patients demonstrated that intestinal Mg^{2+} absorption was preserved, which was indicative for a renal defect (239). Other family members had low serum Mg^{2+} as well, but lacked symptoms of Mg^{2+} deficiency (239, 478). Detailed haplotype analyses identified the segregation of an affected haplotype in the two families, which is suggestive for a common ancestor (478). A recent study reported on two new Belgian and Dutch families with IDH that also shared this haplotype. Indeed, the same mutation was identified in all families (142, 477).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Linkage analysis followed by genetic candidate screening led to the discovery of a mutation in the *FXYD2* gene, resulting in amino acid substitution G41R in the encoded γ-subunit of the Na^+-K^+-ATPase (FXYD2) in the IDH patients (477). The Na^+-K^+-ATPase consists of α- and β-subunits that form a complex for the active transport of Na^+ and K^+ in opposite directions. The γ-subunit is a small, type I transmembrane protein of which the transmembrane domain binds to a groove formed by several helices of the Na^+-K^+-ATPase α-subunit (426). *Xenopus laevis* oocyte studies showed that this association is necessary for transport of the γ-subunit to the plasma membrane, but not for plasma membrane expression of functional Na^+-K^+-ATPase proteins (49). The γ-subunit is suggested to modulate the kinetics of Na^+-K^+-ATPase-mediated transport, with changes in the affinity to ATP or dependence to the membrane potential (23, 48, 49, 426, 584, 742). Expression studies in *Xenopus* oocytes and mammalian cells have shown that the G41R disease mutant is retained in the cytoplasm as it lacks interaction with the Na^+-K^+-ATPase α-β complex (86, 476). It is suggested that the dominant-negative G41R mutant protein can oligomerize with wild-type subunits, thereby abrogating the binding to the Na^+-K^+-ATPase (476). Immunolocalization studies in rat kidney showed that FXYD2 is highly expressed at the basolateral membrane of cells lining the TAL and DCT (23, 481, 584). It is, therefore,

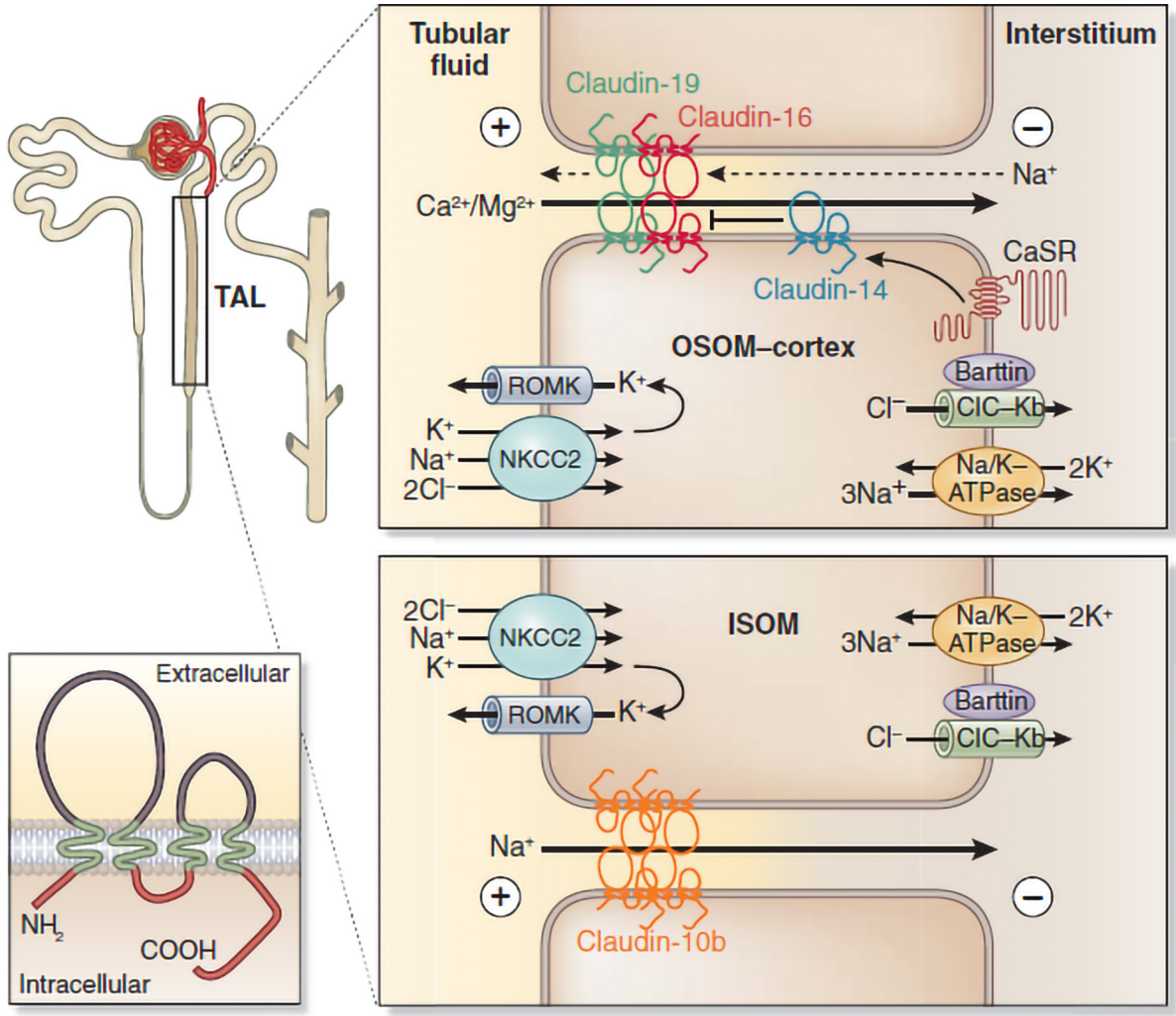


FIGURE 14. Expression and role of claudins in the TAL. Representation of the transcellular and paracellular transport pathways in the thick ascending limb (TAL) cells from the inner stripe of the outer medulla (ISOM) and the outer stripe of the outer medulla (OSOM) and the cortex. Most of K^+ entering the cell via NKCC2 is recycled through ROMK, leading to hyperpolarization of the apical membrane. Cl^- exiting via ClC-Kb is depolarizing the basolateral membrane. The difference in membrane potential constitutes a lumen-positive transepithelial potential that drives paracellular reabsorption of Ca^{2+}/Mg^{2+} and of Na^+. Recent studies have shown that the TAL expresses claudins in a mosaic pattern, with claudins 16/19 predominating in the tight junctions of the cortex and OSOM, whereas tight junctions exclusively made of claudin-10b predominate in the ISOM. This mosaic pattern results in a spatial separation of paracellular Na^+ transport and reabsorption of Ca^{2+} and Mg^{2+}. Tight junctions with claudin-10b favor Na^+ over Mg^{2+}, whereas tight junctions with claudins 16/19 prefer Mg^{2+} over Na^+. As a result, in ISOM TAL, tight junctions with exclusive claudin-10b mediate high paracellular Na^+ permeability, which adds to the transcellular uptake. Reabsorption of Na^+ without water in the ISOM leads to a hyposmotic luminal fluid in the cortical TAL, which may favor Na^+ diffusion from the interstitium into the lumen along its concentration gradient, through tight junctions rich in claudin-10b. *Inset*: general claudin protein and membrane-folding model: 4 transmembrane helical domains (green), 2 extracellular loops (blue), and 1 intracellular loop as well as a short NH_2-terminal and a long COOH-terminal cytoplasmic domain (red). ATPase, adenosine triphosphatase; CaSR, calcium sensing receptor; ClC-Kb, chloride channel Kb; ISOM, inner stripe of the outer medulla; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; OSOM, outer stripe of the outer medulla; ROMK, renal outer medullary K^+ channel. [Adapted from Milatz et al. (485) and Olinger et al. (544), with permission from Elsevier.]

proposed that misrouting of mutant FXYD2 will diminish the functionality of the Na^+-K^+-ATPase in DCT. Hence, reduced intracellular K^+ or increased intracellular Na^+ will lower the membrane potential at the apical membrane resulting in a diminished driving force for Mg^{2+} uptake and subsequent Mg^{2+} wasting.

A heterozygous mutation of the *FXYD2* gene in humans does not lead to hypomagnesemia, pointing towards a specific dominant-negative effect of the G41R mutation in patients with isolated hypomagnesemia (477). Another mechanism of action has been proposed by Sha and co-workers (486, 677), which measured large nonselec-

tive ion currents in FXYD2-expressing oocytes with different characteristics for the G41R mutant. It is, however, not known whether the protein forms an ion channel or indirectly affects other ionic currents. *Fxyd2* KO mice display no abnormalities in urinary Mg^{2+} excretion or serum Mg^{2+} levels (21, 356). Interestingly, they were suspected to have elevated Na^+-K^+-ATPase activity and showed hyperphosphorylation of NCC in kidney (22). This was anticipated to lead to Na^+ retention and hypertension, but the KO mice showed no abnormalities in their Na^+ balance and were normotensive (22). Of note, the mice exhibited a mild pancreatic phenotype with reduced blood glucose and elevated levels of circulating insulin. They showed enhanced glucose tolerance but no insulin resistance (21). Future investigation should unveil the mechanism responsible for these observations and assess these clinical parameters in patients harboring *FXYD2* mutations.

Identification of new causative genes for hypomagnesemia has also shed light on the *FXYD2* gene transcription in DCT. Mutations in the *HNF1B* gene encoding the transcription factor hepatocyte nuclear factor 1β (HNF1β) have been associated with an autosomal dominant disorder named renal cysts and diabetes syndrome (RCAD; MIM no. 137920). The disorder is characterized by maturity-onset diabetes of the young 5 (MODY5) and severe nondiabetic renal dysfunction (308, 525). In 2009, Adalat et al. (6) found that nearly half of the subjects carrying a *HNF1B* mutation present with hypomagnesemia due to renal Mg^{2+} wasting. The association of mutations in *HNF1B* with hypomagnesemia (and other tubular abnormalities) of renal origin has been confirmed in subsequent cohorts, which also evidenced the marked heterogeneity of the clinical presentation (196).

HNF1β is a homeodomain-containing transcription factor expressed in developing mouse ureters and collecting ducts, and postnatally observed in proximal and distal tubules (129, 394). HNF1β regulates the *FXYD2* gene expression (6, 206), at least in vitro, and that may explain its role in renal Mg^{2+} handling. In addition, it was recently identified as transcriptional activator of *KCNJ16*, which encodes the K^+ channel Kir5.1 (397). Mutations in *KCNJ16* are associated with SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance) or EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome, another Mg^{2+} wasting tubulopathy that will be discussed below. Kir5.1 likely plays an important role in Mg^{2+} transport in DCT, but the exact molecular mechanism remains to be elucidated. The study by Kompatscher et al. (397) implies that patients with *HNF1B* mutations have reduced Kir5.1 expression, which could explain the renal Mg^{2+} wasting.

Another recent study reported on three patients with homozygous mutations in the *PCBD1* gene, coding for pterin-4-alpha-carbinolamine dehydratase 1 (PCBD1), suffering from hypomagnesemia, renal Mg^{2+} wasting, and MODY5-like diabetes (205). Previously, recessive *PCBD1* mutations have been linked to transient neonatal hyperphenylalaninemia with primapterinuria and deficient tetrahydrobiopterin (BH4) (HPABH4D) (MIM no. 264070) (124, 743). In fact, PCBD1 acts as an enzyme to regenerate BH4, the cofactor for aromatic amino acid hydroxylases, and also acts as a binding partner of the HNF1 transcription factors (743). The finding that HNF1β forms heterotetrameric complexes with PCBD1 (208, 480) and the in vitro data demonstrated that the HNF1β-PCBD1 complex enhances the FXYD2 promoter provide a putative link between PCBD1 and Mg^{2+} reabsorption in DCT (205) **(FIGURE 13)**.

The latter findings strengthen the idea of the γ-subunit of the Na^+-K^+-ATPase regulating renal Mg^{2+} transport in DCT. They also point to a transcriptional level of regulation in the processes affecting renal Mg^{2+} handling, which needs further investigation.

4. Hypomagnesemia with secondary hypocalcemia

A) BRIEF CLINICAL DESCRIPTION. Initially described in 1968, familial hypomagnesemia with secondary hypocalcemia (HSH, also named hypomagnesemia 1, HOMG1; MIM no. 602014) is a rare recessive disorder that is characterized by severe electrolyte abnormalities shortly after birth (555). Patients suffer from severe hypomagnesemia (Mg^{2+} levels ~0.2 mM) and hypocalcemia, which causes neuromuscular symptoms including seizures and tetany, and they require life-long Mg^{2+} supplementation to overcome these complications. The hypomagnesemia is primarily caused by a defect in Mg^{2+} absorption in the intestine, but there is a renal Mg^{2+} leak as well (470, 658, 786). PTH levels were found to be inappropriately low, which is seen more often in cases of Mg^{2+} deficiency and thought to be the cause of hypocalcemia (217, 483, 628). The Ca^{2+} levels could be not be restored by administration of Ca^{2+} or vitamin D, but Mg^{2+} supplementation is needed (101, 679). Fast diagnosis and immediate treatment are essential to prevent permanent neurological damage or even cardiac arrest.

B) GENETICS. Mutations in the *TRPM6* gene (located on 9q21.13) were identified as the cause of HSH through a positional candidate gene approach (658, 786). *TRPM6* encodes the TRPM6 ion channel, which is a large protein (~2,000 amino acids) belonging to the melastatin subfamily of the transient receptor potential (TRP) family of ion channels (125). In the past decade, mainly NH_2-terminal splice site and frame-shift mutations have been described that lead to a truncated form of TRPM6. Additionally, several missense mutations were identified, which result in loss of channel function (763) **(FIGURE 13)**. Importantly, TRPM6 has a restricted expression pattern along the epithelia of the

kidney and intestine that actively transport Mg^{2+} (780). Together with the finding that it functions as a Mg^{2+}-permeable channel (780), it can explain the severe hypomagnesemia in HSH patients. Of interest, a recent meta-GWAS performed in 7 cohorts amounting to 9,099 individuals identified a common variant in the *TRPM6* locus associated with the urinary Mg^{2+} levels, substantiating the role of TRPM6 in Mg^{2+} homeostasis and metabolism (133).

C) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. A TRPM6 ion channel consists of four subunits, each containing six membrane-spanning domains and large intracellular NH_2 terminal and COOH termini (593, 651). In addition to its function as ion channel, the TRPM6 C-tail comprises a protein kinase domain, which led to the term *chanzyme* (channel and enzyme) (492). The functional link between ion channel and kinase domain is still not completely resolved, but the kinase domain seems to have a modulatory role in channel activity (155, 741, 764, 854). A recent study demonstrated one missense mutation, located in close proximity to the kinase domain (S1754D), which resulted in both loss of channel function and of kinase activity (410a, 764) **(FIGURE 13)**. Yeast two hybrid screens resulted in the identification of the TRPM6 kinase binding partners RACK1 (receptor for activated C kinase 1), REA (repressor of estrogen receptor activity), and MsrB1 (methionine sulfoxide reductase B1) that affect channel function (92–94). TRPM6 likely forms either homomeric complexes or heterotetramers with TRPM7, which influences channel characteristics (429, 854). Several intracellular components like pH, phosphatidylinositol 4,5-bisphosphate, ATP, and Mg^{2+} are also identified as channel regulators (428, 741, 780, 830).

Additional levels of channel regulation involve the transcription and cell surface expression. First, the renal TRPM6 mRNA level was shown to be upregulated in mice fed a Mg^{2+}-deficient diet to maximize renal Mg^{2+} conservation (265). Second, the magnesiotropic hormones EGF and estrogen are involved in the regulation of *TRPM6* mRNA expression (265, 266, 338, 339). Additionally, EGF can affect channel function by increasing the expression of TRPM6 at the plasma membrane through downstream signaling of the EGF receptor, involving the MAPK/extracellular signal-regulated kinase (ERK) pathway and signaling of PI3K and Rac1 (ras-related C3 botulinum toxin substrate 1) (740). Next, insulin was recently identified as the third hormone that plays a role in TRPM6 regulation (508). It can stimulate channel function via the PI3K and Rac1-mediated pathway that enhances cell surface expression of TRPM6 **(FIGURE 13)**. The authors examined two genetic variants in TRPM6 (I1393V and K1584E) that are associated with the total glycosylated hemoglobin level, a measure of insulin resistance, in pregnant women (508). Third, there is an increasing body of evidence for regulation of *TRPM6* mRNA expression in drug-induced hypomagnesemia involving the immunosuppressants cyclosporine A and tacrolimus, loop and thiazide-diuritics, proton pump inhibitors, and the anti-cancer drug cyclosporin (412).

The role of EGF in Mg^{2+} homeostasis has been further substantiated by the association of hypomagnesemia with a mutation in the *EGF* gene. In 1987, Geven et al. (240) reported two sisters with an autosomal recessive form of isolated renal Mg^{2+} loss. Their urinary Mg^{2+} excretion was in the normal range despite low serum Mg^{2+} values (0.53–0.66 mM) and they had no other biochemical abnormalities. Both sisters presented with psychomotor retardation and suffered from epileptic seizures (240). Genetic linkage analysis and subsequent candidate screening led to the identification of a homozygous mutation in *EGF* in this form of renal hypomagnesemia (HOMG4; MIM no. 611718) (266). *EGF* encodes a large membrane-anchored precursor protein, which can be cleaved into pro-EGF that in turn gives rise to the small peptide hormone EGF (39). Importantly, Groenestege et al. (266) demonstrated an overlapping expression of EGF and TRPM6 in DCT, and earlier studies (238, 635) have shown that the EGFR is present along the basolateral membrane of the TAL and DCT. The mutation identified in the two sisters with hypomagnesemia results in a proline to leucine substitution at position 1070 (P1070L) in the cytoplasmic tail of pro-EGF. This is thought to affect a basolateral sorting motif, thereby preventing pro-EGF trafficking and cleavage at the basolateral membrane (266, 290). Hence, the hypomagnesemia is likely caused by failed stimulation of the EGFR at the basolateral membrane due to insufficient secreted EGF. Together with the finding that EGF enhances TRPM6 channel activity, this led to the hypothesis that EGFR signaling plays a key role in renal Mg^{2+} reabsorption. This notion was further supported by clinical studies demonstrating that colorectal cancer patients develop hypomagnesemia due to anti-cancer treatment with the monoclonal EGFR antibody cetuximab (663, 735). Impaired EGF signaling is likely involved in other forms of hypomagnesemia as recent studies suggest that the chemotherapeutic drug cisplatin and the immunosuppressant cyclosporine inhibit renal Mg^{2+} reabsorption via downregulation of the TRPM6-EGF pathway (416, 417). The discovery of EGF as a magnesiotropic hormone has improved the understanding of the molecular mechanisms regulating systemic Mg^{2+} balance.

A mouse model with homozygous deletion of *Trpm6* was found to be embryonic lethal, pointing towards a developmental role of TRPM6 to maintain the Mg^{2+} balance (787, 818). The few *Trpm6* KO mice that were viable upon high-Mg^{2+} diet had defective brain and facial development (787). Additionally, both groups showed that the heterozygous *Trpm6* mice present a mild hypomagnesemia (787, 818). Chubanov et al. (122) recently developed a conditional *Trpm6* KO mouse model. Postnatal inactivation of *Trpm6* led to a shorter lifespan, growth retardation, im-

paired metabolism, and many characteristics that are generally a hallmark of "accelerated aging" (122). Importantly, the phenotype could be rescued by a high-Mg^{2+} diet. In addition to a global KO, Chubanov et al. (122) also generated kidney-specific and intestinal-specific *Trpm6* KO mice. While the conditional inactivation of TRPM6 in the kidney did not result in changes in serum Mg^{2+} levels, disruption of TRPM6 in the intestine led to hypomagnesemia (122). This suggest that TRPM6-mediated Mg^{2+} absorption in the colon is essential for the body's Mg^{2+} balance. Altogether, these investigations yielded crucial informations about the role of TRPM6 in Mg^{2+} homeostasis.

5. Autosomal dominant hypomagnesemia

A) BRIEF CLINICAL DESCRIPTION. In 2009, a new type of hypomagnesemia was identified in a large Brazilian family, with an autosomal dominant form of inheritance (245). The affected individuals present recurrent muscle cramps, tetany, tremor, and muscle weakness, detected from early childhood. Furthermore, a cerebral MRI demonstrated a slight atrophia of the cerebral vermis in one patient, and electromyographs of more affected family members indicated involuntary muscular movements called myokymia. Serum Mg^{2+} levels were low, while other electrolyte levels were in the normal range and there was no change urinary Mg^{2+} excretion indicative of a renal defect. Importantly, the proband also showed facial myokymia and intermittent tetanic contraction, which improved shortly after Mg^{2+} administration. Electromyographs of some affected family members showed myokymic discharge. A daily Mg^{2+} supplementation could improve the observed symptoms in the affected family members.

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. A positional cloning approach led to the identification of a heterozygous mutation in the *KCNA1* gene (12p13.32), coding for the Shaker-related voltage-gated K^+ channel Kv1.1, in the affected family members (245). Kv1.1 functions as a tetrameric structure, and each subunit consists of six transmembrane segments (S1-S6), of which S4 acts as a voltage sensor and a pore region is formed by S5 and S6. The mutation results in an amino acid substitution (N255D) localized close to S3. Electrophysiological analysis demonstrated a dominant-negative effect of the mutation on wild-type Kv1.1 channel function (245). Recently, a second (de novo) *KCNA1* mutation was reported in a patient with tetany and hypomagnesemia. This L328V mutation also led to a dominant-negative loss of function of the encoded Kv1.1 channel (765). Immunohistochemistry showed Kv1.1 localization at the luminal membrane of DCT cells (97, 245), which suggests a potential link between Kv1.1-mediated K^+ efflux and Mg^{2+} reabsorption. The hypothesis arose that Kv1.1 is involved in the maintenance of the membrane potential across the apical membrane that functions as the driving force for Mg^{2+} uptake via TRPM6 **(FIGURE 13)**. Hence, the mutation may reduce this electrical gradient and therefore results in diminished Mg^{2+} transport and subsequent renal Mg^{2+} wasting.

Mutations in *KCNA1* had previously been associated with episodic ataxia type 1 (EA1) (MIM no. 160120), a dominant neurological disorder caused by defective Kv1.1 channels in the cerebellum (84, 260). Despite similar loss in Kv1.1 function, hypomagnesemia has not been reported in these cases, and it would, therefore, be of interest to investigate the plasma Mg^{2+} levels in this group of patients with *KCNA1* mutations. Next to this, *Kcna1* null mice (696) or *Kcna1* KI mice (85) that are currently studied to explain the epileptic seizures could be examined for Mg^{2+} wasting. It is generally known that a voltage-dependent K^+ secretion occurs along the distal tubule, which results in the lumen-positive membrane potential favoring Mg^{2+} uptake. However, it should be noted that other candidates than Kv1.1 have been proposed, including the ROMK and Maxi-K (or BK) channels (717). Future studies should reveal the exact components of K^+ secretion in DCT and its role in K^+ and Mg^{2+} homeostasis.

6. SeSAME/EAST syndrome

A) BRIEF CLINICAL DESCRIPTION. In 2009, two independent groups reported a new syndrome characterized by seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME) (62, 661). This association is also termed EAST syndrome (epilepsy, ataxia, sensorineural deafness, and a renal salt-losing tubulopathy) and has an autosomal recessive pattern of inheritance (MIM no. 612780). The patients presented with neurological symptoms from young age, including seizures, pronounced ataxia, and delayed psychomotor development. Some infants were unable to walk until the age of 3–9 yr. These neurological manifestations are the most invalidating aspect of the disease (1). Further laboratory analyses of the renal salt-losing tubulopathy showed hypokalemic metabolic alkalosis and hypomagnesemia, together with increased urinary excretion of K^+, Mg^{2+}, and Na^+. In addition, the levels of renin and aldosterone were increased without signs of hypertension. These features are similar to those associated with Gitelman syndrome. There is significant phenotypic heterogeneity and intrafamilial variability in the SeSAME/EAST syndrome (1). Patients receive salt, K^+, and Mg^{2+} supplementation to control their electrolyte levels (62, 661).

B) GENETICS, PROTEIN FUNCTION, AND INSIGHTS FOR RENAL PHYSIOLOGY. Whole-genome linkage analysis followed by candidate screening and sequencing revealed several missense mutations in *KCNJ10* (location 1q13.2) that encodes the K^+ channel Kir4.1 (62, 661). It belongs to the inward rectifier K^+ channel family and is expressed in the brain, inner ear, and kidney (12, 341, 731), which can explain the pleiotropic phenotype seen in patients. Kir4.1 localizes to the basolateral membranes of DCT and more distal nephron parts

(341). Here, heterotetrameric complexes of Kir4.1 and Kir5.1 likely represent the main K^+ channel functioning as a K^+ recycling mechanism needed for Na^+-K^+-ATPase activity (447, 851). The disease-causing mutations are shown to affect the function of both homomeric and heteromeric channels, either by mistrafficking or by altered channel characteristics (218, 550, 597, 634, 733, 811).

Studies performed in *Kcnj10* KO mice demonstrated an early lethality due to neurological complications such as seizures (516). Importantly, the renal phenotype in the neonates closely resembles that seen in SeSAME/EAST patients (62). In contrast, mice with deletion of *Kcnj16* (encoding Kir5.1) showed no difference in survival or growth compared with wild type, and the adult mice developed hypokalemic metabolic acidosis and hypercalciuria, contrasting with the SeSAME/EAST syndrome phenotype (554). Furthermore, Paulais et al. (554) demonstrated an increased basolateral K^+ conductance in DCT of *Kcnj16* KO mice, which suggests that homomeric Kir4.1 channels can maintain the transport function in DCT. In line with earlier studies (732, 832), these channels have an increased activity and a milder intracellular pH (pH_i) sensitivity compared with Kir4.1/Kir5.1 channels (554). This implies that variations in pH_i can produce significant changes in basolateral K^+ conductance and highlights the role of Kir5.1 in renal ion transport by Kir4.1 heteromerization. More recently, Cuevas et al. (139) generated an inducible kidney-specific *Kcnj10* KO line. These mice exhibited metabolic alkalosis and hypokalemia, combined with hypocalciuria and hypermagnesiuria. Further evidence for the role of Kir4.1 in sensing plasma K^+ levels came from the abrogated phosphorylation of NCC upon low dietary K^+ in these kidney-specific *Kcjn10* KO mice (139). As noted above, NCC expression and activity are highly sensitive to plasma K^+ levels, which can even dominate the effects of aldosterone or extracellular fluid volume on the DCT (736, 737). Terker et al. (737) demonstrated that NCC is regulated by the WNK/SPAK signaling pathway in response to changes in plasma K^+, through effects on membrane voltage in the DCT. The latter is controlled by Kir4.1, and likely Kir5.1, channels at the basolateral membrane, thereby demonstrating the molecular mechanism underlying the salt-wasting phenotype of SeSAME/EAST syndrome (804) **(FIGURE 11)**.

Yet, the exact mechanism that underlies decreased Mg^{2+} reabsorption (and hypermagnesiuria) in SeSAME is still not completely understood. Loss of Kir4.1 activity impedes Na^+-K^+-ATPase transport that in turn leads to depolarization of the basolateral membrane. The net effect is a diminished driving force for electrogenic transport via the putative Na^+/Mg^{2+} exchanger, thereby disturbing the Mg^{2+} transport gradient. However, it likely also diminishes the Cl^- efflux by Cl^- channels: a recent report by Zhang et al. postulated that subsequent activation of SPAK-dependent pathways plays an important role in the development of electrolyte disturbances (851). They demonstrated a reduced NCC expression in *Kcnj10* KO mice (851), which could lead to diminished TRPM6 expression as observed previously in *Slc12a3*-null mice and thiazide-treated rats (524, 665). Furthermore, analysis of dissected DCT tubules showed a depolarized membrane potential in *Kcnj10* KO (global and kidney-specific) animals compared with wild type, which would hamper TRPM6-mediated Mg^{2+} transport (139, 851). The hypokalemia and alkalosis result from increased salt delivery to the CNT and CCD, which increases Na^+ reabsorption by ENaC and K^+ and H^+ secretion. Overall, identification of Kir4.1 as the genetic factor of this multi-faceted syndrome has established a key role of basolateral K^+ transport in regulating distal tubular electrolyte transport.

7. Hypomagnesemia with seizures and mental retardation.

A) BRIEF CLINICAL DESCRIPTION AND GENETICS. Two unrelated families with a dominant form of renal hypomagnesemia (HOMG6) (MIM no. 613882) were screened for the causative gene of their Mg^{2+} wasting phenotype. Patients presented with muscle weakness, tremor, seizures, and headaches as a result of the low Mg^{2+} serum concentrations (0.3–0.5 mM), and had no other electrolyte disturbances detected (479, 716). Heterozygous mutations were identified in the *CNNM2* gene, which codes for the protein named cyclin and CBS domain divalent metal cation transport mediator 2 (CNNM2) (716). In addition to this finding, a recent report described five new families in which *CNNM2* mutations were linked to a distinct phenotype of hypomagnesemia with mental retardation and seizures (HOMGSMR1; MIM no. 616418) (19). Patients were diagnosed at early childhood and had a severe degree of psychomotor retardation. Mg^{2+} supplementation only moderately restored the serum Mg^{2+} levels, and seizures were suppressed by the use of anti-epileptic drugs. Of note, the brain phenotype and intellectual disability were most severe in patients carrying recessive mutations and could not be improved by Mg^{2+} supplementation (19).

B) PROTEIN FUNCTION AND INSIGHTS FOR RENAL PHYSIOLOGY. CNNM2 was originally characterized as a member of the ancient conserved domain protein (ACDP) family, consisting of four members that share structural homology to cyclin proteins and have been listed as putative Mg^{2+} transporters (259, 791, 835). Additionally, common variants in the *CNNM2*, *CNNM3*, and *CNNM4* genes have been associated with serum Mg^{2+} concentrations in a GWAS study (482). CNNM2 has a ubiquitous expression pattern with highest abundance in kidney, brain, and lung (143, 791). Within the kidney, CNNM2 is mainly localized along the basolateral membrane of DCT, which raised the notion that it could be an unidentified Mg^{2+} extruder (143, 716). Further evidence for a role of CNNM2 in Mg^{2+} handling appeared from microarray

analysis of mouse DCT cells demonstrating Mg^{2+}-responsive gene regulation of the *CNNM2* gene (259). Interestingly, heterozygous and kidney-specific homozygous *Cnnm2* KO mice show hypomagnesemia, supporting a possible role of CNNM2 in renal Mg^{2+} handling (222).

However, the exact function of CNNM2 is still unclear. While Mg^{2+} currents could be evoked by overexpression in *Xenopus* oocytes (259), patch clamp and Mg^{2+} imaging experiments in mammalian cells did not demonstrate direct Mg^{2+} transport. Therefore, a regulatory role for CNNM2 in Mg^{2+} sensing was proposed (19, 716). Arjona et al. (19) showed an increased Mg^{2+} uptake upon overexpression of CNNM2, which was abrogated in the CNNM2 disease mutants. The examined mutants failed to reach the plasma membrane (19). In addition, knock-down of *cnnm2* in zebrafish decreased the body Mg^{2+} content, and it could be recovered by expressing the wild-type CNNM2, but not by a disease mutant of CNNM2 (19).

Structurally, CNNM2 contains five putative transmembrane segments and an extracellular COOH terminus, which holds two cystathionine β-synthase (CBS) domains that can form a dimer (716). Initial homology modeling of these CBS domains, based on the CorC protein, showed conservation of a potential Mg^{2+}-ATP binding site that encloses the disease-causing T568I mutation (143). This finding was recently confirmed by the resolved crystal structure that revealed conformational changes of the CBS dimer upon nucleotide binding (132). The CBS domains of CNNM2 indeed bind ATP, but not AMP, in a Mg^{2+}-dependent manner (300). Moreover, the T586I mutation was shown to hinder nucleotide binding and lock the CBS module, thereby rendering the protein in a nonfunctional state (132, 300). This failure may directly impair Mg^{2+} transport across the basolateral membrane, or indirectly by altering the regulation of other basolateral transporters in the DCT. A suggested mechanism of action is an incorrect sensing of the intracellular Mg-ATP levels.

Identification of mutations in *CNNM2* associated with hypomagnesemia shed light on the basolateral Mg^{2+} extrusion mechanism in the DCT. The recently resolved crystal structure will facilitate future studies to clarify the exact function of CNNM2 in DCT-regulated Mg^{2+} transport (132). In addition, CNNM2 should be considered an important factor in brain development, since the neurological phenotype observed in the patients with *CNNM2* mutations could not be attributed to Mg^{2+} status. Of note, genetic variants in *CNNM2* have been associated with schizophrenia in large population studies (269, 656).

IV. OUTLOOK AND PERSPECTIVES

Twenty-five years after the identification of the first gene involved in an inherited kidney tubular disease, NGS, multi-omics technologies, deep-phenotyping of model organisms combined with clinical studies and multicentric efforts to gather patient cohorts and to create registries and biobanks have yielded an unprecedented amount of informations that are directly relevant for our understanding of fundamental processes operating in health and disease. In turn, these insights proved valuable for refining disease ontology, improving diagnosis and follow-up, and providing new therapeutic targets in a number of rare kidney disorders (159).

The rare disorders discussed in this review illustrate the path between clinical description, gene discovery, mechanistic studies, and translational applications. These diseases involve various genetic mechanisms and modes of inheritance; they affect a large variety of cellular processes operating in distinct tubular segments of the kidney; most often, they have multi-systemic complications; they involve channels, transporters, receptors, enzymes, structural proteins, regulatory subunits, and transcription factors, all participating in transcellular and paracellular transport pathways **(TABLE 1, FIGURE 2)**. The genetic and mechanistic insights contributed to better understand the action, or side effects, of known drugs, but also to improve existing therapies or to develop new ones. They thus proved valuable in addressing the ultimate challenge— closing of the gap between genetic and mechanistic understanding and drug development for rare diseases.

These advances have left many open questions, which are currently investigated using increasingly efficient and affordable tools. The advent of NGS and multiplex testing, allowing the simultaneous investigation of all relevant genes for a given phenotype at reduced costs and turnaround times (24), will increase diagnosis efficiency for inherited kidney disorders. In turn, the newly identified cases will precise the genotype-phenotype correlations and the clinical manifestations, sometimes unsuspected or surprising, associated with a given syndrome, yielding new information about the role of the mutant protein in a given tissue (27, 56, 159, 167). The increasing availability of affordable whole exome or even whole genome sequencing should have broad consequences for our understanding of the genetic architecture of kidney disease. The number of unresolved cases should decrease, substantiating the genetic heterogeneity of some disorders (e.g., Dent disease) or clarifying the missing allele in some recessive disorders (e.g., Gitelman syndrome). These new genes, associated with multi-omics profiles (including transcriptomics, epigenomics, metabolomics, proteomics) and improved model organisms based on new genome editing technologies, induced pluripotent stem (iPS) cells, and human kidney organoids (279, 498, 565, 727, 728) or direct reprogramming (367), will drive multilevel analysis of cellular mechanisms and improve the ontology of disease. Another benefit of the sequencing technologies will be the discovery of common and rare genetic variants that could act as modifier genes,

helping to decipher the significant intrafamilial variability observed in many rare disorders, or explain the individual sensitivity to some drugs. These analyses should also substantiate the continuum of genetic kidney disease risk, with important genes involved from rare Mendelian disorders to common variation in the general population (163, 828). Information on the carrier state (for a recessive or *X*-linked disorder) will be important, not only for genetic counseling, but also for clinical implications and, more generally, selection mechanisms and evolutionary perspectives (159, 353, 387, 625).

Important physiological questions linked to the diseases discussed here include mechanisms and regulators of membrane trafficking, maintenance of epithelial cell differentiation, biogenesis of intracellular vesicular compartments, signaling pathways downstream of apical and basolateral receptors and cross-talk between membrane compartments, flow-mediated regulation of apical receptors and transport processes, functional segmentation and capacity of adaptation of specific tubular segments, and mechanisms of transcriptional regulation in tubular cells (160, 194, 544). Downstream of gene and mechanistic pathways, translational studies will have to address issues including the unexplained differences between human and mouse phenotypes (e.g., mouse models for Dent disease, Gitelman syndrome, claudin disorders), variable manifestations of tubular dysfunction in similar disorders (e.g., PT dysfunction and RFS), and the links between tubular dysfunction and the development of CKD.

Finally, the continuum between rare kidney diseases and more common disorders should be substantiated. For instance, some genes involved in the tubular handling of salt (*SLC12A3*, *KCNJ1*, *SLC12A1*, *UMOD*) are also relevant for blood pressure control as shown by analysis of the carrier state (353) or by GWAS for blood pressure in the population (547). Genes encoding the megalin (*LRP2*) and cubilin (*CUBN*) receptors, and the adaptor protein Dab-2 (*DAB2*), that mediate endocytosis of ultrafiltered LMW proteins in the proximal tubule and are defective in rare disorders were shown by GWAS to affect renal function and risk of CKD (74, 450, 553). The genes *SLC2A9* (GLUT9) and *SLC22A12* (URAT1), which are associated with hereditary renal hypouricemia, were also pointed in GWAS on serum urate concentration (395, 405). Genes involved in rare disorders of Ca^{2+} and Mg^{2+} handling (*CASR*, *TRPM6*, *CLDN14*, *CNNM2*) have also been associated with Ca^{2+} and Mg^{2+} homeostasis and metabolic traits in the general population (133, 134, 371, 482, 716). The characterization of the biological mechanisms sustaining the effect of rare and common variants in these genes or in additional genes identified by GWAS will undoubtedly provide further insights into the biological mechanisms sustaining kidney function.

ACKNOWLEDGMENTS

We acknowledge all the members of our teams and collaborators who contributed over the years to studies of inherited kidney disorders. We apologize for the many contributions that could not be referenced due to the scope of coverage. We particularly thank Dennis Brown (Harvard Medical School, Boston, MA) for supporting this review topic over the years.

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GRANTS

O. Devuyst is supported by the Swiss National Centre of Competence in Research Kidney Control of Homeostasis (NCCR Kidney.CH) program; the Swiss National Science Foundation (31003A_169850); the Rare Disease Initiative Zurich (Radiz), a clinical research priority program of the University of Zurich, Switzerland; the Fonds National de la Recherche Scientifique and the Fonds de la Recherche Scientifique Médicale (Brussels, Belgium); the European Community's Seventh Framework Programme under Grant 305608 (EURenOmics); and the Cystinosis Research Foundation (Irvine, CA, USA). J. van der Wijst is supported by European Union's Horizon 2020 Marie Skłodowska-Curie Grant 748058 and by The Netherlands Organisation for Health Research and Development Off Road Grant 451001 004.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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