Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., Editor

GENETIC DISORDERS OF RENAL ELECTROLYTE TRANSPORT

STEVEN J. SCHEINMAN, M.D., LISA M. GUAY-WOODFORD, M.D., RAJESH V. THAKKER, M.D., AND DAVID G. WARNOCK, M.D.

In the 1950s and 1960s, several inherited disorders of fluid and electrolyte metabolism were described in which the principal disturbance appeared to be a specific functional defect in the renal tubule. For most of these diseases, plausible physiologic explanations were presented, some more convincing than others. In the past five years, genetic and molecular approaches have elucidated the underlying molecular defects in several of these disorders. In some instances, predictions based on the initial physiologic studies have been confirmed; in others, the molecular answer has come as a surprise, raising further questions about the physiology of epithelial function. In several cases, the discovery of the molecular defect in a rare mendelian disorder has provided important insights into complex traits, such as hypertension and hypercalciuria.

A variety of inherited disorders alter specific renal epithelial transport functions (Table 1). This review addresses those in which the transport of electrolytes or minerals by the renal tubular epithelium is deranged and the defect has been attributed to a specific transport protein. This review does not include disorders in which the principal disturbance involves the transport of bicarbonate or protons (e.g., renal tubular acidosis). The disorders reviewed and the nephron segments affected are shown in Figure 1.

MUTATIONS AFFECTING THE EPITHELIAL SODIUM CHANNEL

Liddle's Syndrome

In 1963 Liddle and colleagues described a familial syndrome of severe hypertension, hypokalemia, and metabolic alkalosis that mimicked hyperaldosteronism. Clinical studies revealed that affected patients had exceptionally low rates of aldosterone secretion, hyporeninemia, no response to spironolactone, and a response to triamterene and salt restriction. Liddle et al. stated, “The disorder apparently stems from an unusual tendency of the kidneys to conserve sodium and excrete potassium even in the virtual absence of mineralocorticoids.” This mechanism was confirmed by the fact that the disorder resolved after renal transplantation in the proband, in whom renal failure had developed 25 years after the original study. Studies of the original pedigree revealed an autosomal dominant mode of inheritance; ultimately, mutations affecting the cytosolic tail of the β subunit of the epithelial sodium channel were found in this and four other, smaller kindreds.

These mutations cause constitutive activation of the epithelial sodium channel in the luminal membrane of the collecting tubule (Fig. 2) and provide a pathophysiologic basis for this rare form of low-renin hypertension. Unregulated reabsorption of sodium across the collecting tubule results in volume expansion, inhibition of renin and aldosterone secretion, and hypertension. Similar activating mutations have been described that affect the γ subunit of the epithelial sodium channel and, more recently, a similar proline-rich region of either the β or the γ subunit, which also result in constitutive activation of the sodium channel, with the same pathophysiologic effects. This proline-rich region interacts with cytoskeletal proteins that may regulate the expression of the channel complex at the luminal membrane.

Although the precise mechanism of the constitutive activation in Liddle’s syndrome is still debated (increased dwelling time in the plasma membrane vs. direct kinetic activation), it is certain that the interaction of the epithelial sodium channel with cytoskeletal proteins regulates its activity. The lack of down-regulation of the epithelial sodium channel in the face of persistent volume expansion underlies the pathophysiology of this syndrome. A similar lack of down-regulation of the activity of the epithelial sodium channels may underlie more common forms of low-renin hypertension. Although truncating or other activating mutations of the genes for the sodium-channel subunits are uncommon in patients...
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*Entries in italics indicate that the mode of inheritance or associations have not been firmly established.
†OMIM denotes Online Mendelian Inheritance in Man (also at http://www.ncbi.nlm.nih.gov/Omim/).
with hypertension, there may be polymorphisms in the channel proteins that have more subtle, yet potentially important, effects on the regulation of epithelial sodium-channel activity.\textsuperscript{11,12}

**Pseudohypoaldosteronism Type I**

There are also clinical syndromes that reflect the loss of sodium-channel activity. One is a familial form of mineralocorticoid resistance known as pseudohypoaldosteronism type I that is associated with renal salt wasting; high concentrations of sodium in sweat, stool, and saliva; hyperkalemia and increased plasma renin activity; and high serum aldosterone concentrations.\textsuperscript{13} This autosomal recessive disorder involves multiple organ systems and is especially marked in the neonatal period, with vomiting, hyponatremia, failure to thrive, and occasionally the respiratory distress syndrome. Respiratory tract infections are common in affected children and may be mistaken for cystic fibrosis.\textsuperscript{14} With aggressive salt replacement and control of hyperkalemia, these children can survive, and the disorder appears to become less severe with age.

The genes encoding the three subunits of the epithelial sodium channel were obvious candidates for involvement in this disorder, and indeed, mutations that cause loss of function of the epithelial sodium channel have been described in each of the subunit genes.\textsuperscript{15,16} In addition, deletion of the $\alpha$ subunit in mice causes death from respiratory distress in the neonatal period,\textsuperscript{17} presumably from the failure to clear alveolar fluid at the time of birth. If these mice are “rescued” from the respiratory failure by the engineered expression of the gene for the $\alpha$ subunit of the epithelial sodium channel in the lung, the mice survive and have salt wasting and hyperkalemia.\textsuperscript{18}

There was initially some confusion in the descriptions of pseudohypoaldosteronism because of uncertainty about its inheritance and reports that there were defects in the mineralocorticoid receptor in some kindreds. This issue has been clarified with the description of four mutations affecting the epithelial sodium channel in the recessive form of pseudohypoaldosteronism type I and of four different mutations affecting the mineralocorticoid receptor in the autosomal dominant form.\textsuperscript{19} These patients present with salt wasting and hyperkalemia but do not have pulmonary or other organ-system involvement. This result was anticipated by the finding that carbenoxolone, which inhibits $11\beta$-hydroxysteroid dehydrogenase type II, the enzyme that converts cortisol to cortisone, can partially correct the apparent mineralocorticoid receptor in certain patients.\textsuperscript{14} By slowing the conversion of cortisol to cortisone, carbenoxolone raises the intracellular cortisol concentration sufficiently to maintain activation of the wild-type receptor, thus overcoming the functional defect in the mutant receptor. This mechanism is consistent with the presence of haploinsufficiency of the wild-type mineralocorticoid

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**Figure 1. Nephron Segments Affected by Genetic Disorders for Which the Gene Has Been Cloned.**

Proximal tubular function is altered by mutations affecting the PHEX (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) protein in X-linked hypophosphatemic rickets, in which reabsorption of phosphate and hydroxylation of vitamin D are abnormal, and by mutations affecting the renal CIC-5 chloride channel in Dent’s disease. CIC-5 is also expressed in the thick ascending limb of Henle’s loop. In Bartter’s syndrome there are mutations in the genes encoding the membrane transport proteins: sodium–potassium–2-chloride transporter (NKCC2), the ATP-regulated potassium channel, and kidney-specific chloride channel CIC-Kb. These genes are expressed in the cells of the thick ascending limb. Mutations in the gene encoding the sodium–chloride transporter in the distal convoluted tubule cause Gitelman’s syndrome. Mutations in the gene encoding the calcium-sensing receptor alter the function of the ascending limb of Henle’s loop and the collecting duct and cause familial hypocalciuric hypercalcemia. Activating mutations in the gene encoding the epithelial sodium channel in Liddle’s syndrome stimulate the reabsorption of sodium chloride in the collecting duct, and inactivating mutations in the genes encoding the epithelial sodium channel or the mineralocorticoid receptor give rise to pseudohypoaldosteronism type I.
receptor in this autosomal dominant form of pseudo-
hypoaldosteronism, whereas the multiorgan defects in
the recessive form are explained by loss-of-function
mutations in the genes for subunits of the epithelial
sodium channel.

**MUTATIONS AFFECTING DIURETIC-
SENSITIVE SODIUM-TRANSPORT
PROTEINS**

**Bartter’s Syndrome**

In 1962 Bartter and colleagues described hypoka-
elmic, hypochloremic metabolic alkalosis in two chil-
dren and a man.20 Other characteristics of the disorder
are increased urinary excretion of potassium and
prostaglandins, normal or low blood pressure despite
increased plasma renin activity and high serum al-
dosterone concentrations, a relative vascular resis-
tance to the pressor effects of exogenous angiotensin
II, and hyperplasia of the juxtaglomerular appar-
atus.20,21 In most patients, the disease is diagnosed in
infancy, childhood, or early adolescence. There is no
predilection with respect to race, ethnic group, or sex.
Although many cases appear to be sporadic, Bartter’s
syndrome does occur in families, with an autosomal
recessive mode of inheritance.21

Bartter’s syndrome is not a single disease but a set
of closely related renal tubular disorders. At least
three phenotypic subgroups have been identified: an
antenatal hypercalcicuric variant, also termed hyper-
prostaglandin E syndrome, which is characterized by
hydramnios, prematurity, and dehydration at birth;
classic Bartter’s syndrome, which presents in chil-
dren, often as failure to thrive; and a hypocalciuric–
hypomagnesemic variant known as Gitelman’s syn-

![Figure 2. Aldosterone-Regulated Transport in the Cortical Collecting Tubule.](image)

Mineralocorticoids regulate electrolyte balance through their
action in the principal cells of the cortical collecting tubule. The
type I mineralocorticoid receptor binds both aldosterone and
cortisol, but not cortisone. The specificity of the receptor for
aldosterone is mediated by the type II kidney isoform of 11β-
hydroxysteroid dehydrogenase (not shown), which converts
cortisol to cortisone. Under normal conditions, the epithelial
sodium channel is the rate-limiting barrier for the entry of sodi-
mum from the lumen into the cell (Panel A). The resulting lumen-
negative transepithelial voltage (indicated by the minus sign)
drives potassium secretion from the principal cells and proton
secretion from the intercalated cells (not shown). In Liddle’s
syndrome, mutations in the gene encoding the epithelial sodium
channel result in persistent unregulated reabsorption of so-
dium and increased secretion of potassium (not shown). In au-
tosomal recessive pseudohypoaldosteronism type I (Panel B),
loss-of-function mutations in this gene inactivate the channel.
In autosomal dominant pseudohypoaldosteronism type I (Pan-
el C), mutations in the gene encoding the mineralocorticoid re-
ceptor disrupt mineralocorticoid regulation of the activity of
the epithelial sodium channel. Either mechanism reduces the
activity of the epithelial sodium channel, thus causing salt
wasting and decreasing the secretion of potassium and protons.
drome, which often presents in adults. This heterogeneity and the diverse array of physiologic derangements long confounded efforts to understand the fundamental defects in these syndromes. Proposed primary defects included juxtaglomerular hyperplasia; insensitivity to angiotensin II; overproduction of prostaglandins, kallikrein, and kinins; a defect in potassium transport resulting in excessive urinary potassium excretion; and a defect in sodium chloride transport in the thick ascending limb of Henle’s loop or the distal convoluted tubule. Among the causes of hypokalemic metabolic alkalosis, the absence of hypertension rules out primary mineralocorticoid excess, and the finding of high urinary chloride excretion rules out secondary hyperaldosteronism due to extrarenal fluid loss. These findings occur only in Bartter’s syndrome and with long-term diuretic therapy. These and other clinical data suggested that Bartter’s syndrome results from defective transepithelial transport of sodium chloride in the thick ascending limb of Henle’s loop. The genes encoding several proteins of the thick ascending limb have been cloned, including the genes encoding the bumetanide-sensitive sodium–potassium–2-chloride transporter (NKCC2), the apical ATP-regulated potassium channel (ROMK), and the kidney-specific basolateral chloride channel (ClC-Kb). Loss-of-function mutations in the genes for each of these transport proteins have been documented in some, but not all, patients with antenatal Bartter’s syndrome or the more classic phenotype.

As shown in Figure 3, sodium chloride transport in the thick ascending limb involves a complex interplay of transporters and channels. Defects in any of these proteins could impair the net reabsorption of sodium chloride in the thick ascending limb and thereby increase delivery of sodium chloride to more distal nephron segments, with consequent salt wasting, volume contraction, and stimulation of the renin–angiotensin–aldosterone axis, leading to hypokalemic metabolic alkalosis. Hypokalemia, chronic volume contraction, and high plasma concentrations of angiotensin, kallikrein, kinins, and vasopressin all stimulate the production of prostaglandin E2. Thus, stimulation of renal and systemic production of prostaglandin E2, which is especially marked in antenatal Bartter’s syndrome, is likely to be secondary to the underlying defect in the transport of sodium chloride in the thick ascending limb.

Impaired transport of sodium chloride in the thick ascending limb is associated with a reduction in the lumen-positive electrical transport potential that normally drives the paracellular reabsorption of calcium and magnesium (Fig. 3), causing increased urinary loss of these ions. Hypercalciuria is a common feature of Bartter’s syndrome and often leads to nephrocalcinosis in antenatal Bartter’s syndrome. Hypomagnesemia, in contrast, is uncommon.

**Gitelman’s Syndrome**

Gitelman’s syndrome is a variant of Bartter’s syndrome in which patients have hypomagnesemia and hypocalciuria. Thiazide diuretics inhibit the sodium–chloride transporter NCCT (also known as the thiazide-sensitive cotransporter) in the distal convoluted tubule (Fig. 4), and patients with Gitelman’s syndrome have a subnormal natriuretic response to intravenous furosemide. Mutations associated with a putative loss of function of the sodium–chloride transporter NCCT have been identified in patients with Gitelman’s syndrome. Loss of function of this sodium–chloride transporter causes defective reabsorption of sodium chloride in the distal convoluted tubule, which normally reabsorbs about 7 percent of the filtered load of sodium chloride. This defect increases solute delivery to the collecting tubule, with consequent mild volume contraction and aldosterone-stimulated secretion of potassium and protons, resulting in mild hypokalemic metabolic alkalosis. The volume contraction, the stimulation of vasopressin and the renin–angiotensin–aldosterone axis, and the potassium depletion appear to be less marked than in Bartter’s syndrome and are not sufficient to increase the production of renal and systemic prostaglandin E2, substantially. Urinary prostaglandin excretion remains normal in patients with Gitelman’s syndrome.

Pharmacologic inhibition of the function of the sodium–chloride transporter by thiazides stimulates the reabsorption of calcium by the distal convoluted tubule, and the mutations that inactivate this transporter in Gitelman’s syndrome presumably cause hypocalciuria in the same manner (Fig. 4). Thiazides limit the entry of sodium chloride across the luminal membrane of the cells of the distal convoluted tubule, and intracellular chloride continues to exit through basolateral chloride channels. This hyperpolarizes the cell and stimulates the entry of calcium through apical, voltage-activated calcium channels. The impairment of sodium entry also lowers the intracellular sodium concentration and facilitates the exchange of sodium for calcium across the basolateral membrane. Thus, thiazides cause changes in both the luminal entry of calcium and the basolateral exit of calcium that increase the reabsorption of calcium in the distal convoluted tubule, with resultant hypocalciuria.

**Magnesium Excretion in Bartter’s and Gitelman’s Syndromes**

Diuretics and mutations causing inactivation of the transport proteins have similar effects on the excretion of sodium chloride and calcium, but not on magnesium excretion. Loop diuretics increase urinary magnesium excretion, whereas thiazides have little effect on it. Most patients with Gitelman’s syndrome...
Sodium chloride is reabsorbed in the thick ascending limb by the bumetanide-sensitive sodium–potassium–2-chloride transporter (NKCC2). This electroneutral transporter is driven by the low intracellular sodium and chloride concentrations generated by Na+/K+–ATPase and the kidney-specific basolateral chloride channel (CIC-Kb). The availability of luminal potassium is rate-limiting for NKCC2, and recycling of potassium through the ATP-regulated potassium channel (ROMK) ensures the efficient functioning of NKCC2 and generates a lumen-positive transepithelial potential. Genetic studies have identified putative loss-of-function mutations in the genes encoding NKCC2, ROMK, and CIC-Kb in subgroups of patients with Bartter’s syndrome. In contrast to the normal condition (Panel A), loss of function of NKCC2 (Panel B) impairs reabsorption of sodium and potassium. Inactivation of the luminal ROMK (Panel C) limits the amount of potassium available for NKCC2. Inactivation of the basolateral CIC-Kb (Panel D) reduces transcellular reabsorption of chloride. Loss of function of any of these transporters will reduce the transepithelial potential and thus decrease the driving force for the paracellular reabsorption of cations. In most patients with Bartter’s syndrome, urinary calcium excretion is increased. Activation of the calcium-sensing receptor (CaR) inhibits activity of the ROMK potassium channel and thereby reduces the reabsorption of solutes in this nephron segment.29
have increased urinary magnesium excretion and marked hypomagnesemia, but in patients with Bartter’s syndrome, hypomagnesemia is uncommon and, when present, mild. The physiologic basis for these differences in magnesium excretion is not known.

In mammals about 60 percent of filtered magnesium is normally reabsorbed in the thick ascending limb, and 5 to 10 percent is reabsorbed in the distal convoluted tubule; there is very little reabsorption of magnesium in the collecting duct. The mechanisms for the reabsorption of magnesium in the distal convoluted tubule are similar to those for calcium reabsorption and include a luminal magnesium channel and a basolateral sodium–magnesium exchanger. In addition, there may be specific magnesium transporters that have not yet been identified. Volume depletion, metabolic alkalosis, and vasopressin stimulate magnesium transport in the distal convoluted tubule, and aldosterone can potentiate this effect of vasopressin. These hormonal actions appear to be counterbalanced by the effects of potassium depletion, which inhibits the reabsorption of magnesium in the distal convoluted tubule.

On the basis of these physiologic observations, we propose that net magnesium excretion is determined by the balance of hormonal effects and intracellular potassium stores in the distal convoluted tubule. Thus, the marked salt wasting and aldosterone stimulation in patients with antenatal or classic Bartter’s syndrome may stimulate the reabsorption of magnesium in the distal convoluted tubule, substantially mitigating the magnesium wasting caused by the transport defect in the thick ascending limb. Since loop diuretics are short-acting, there may be less stimulation of magnesium reabsorption in the distal convoluted tubule in patients treated with these drugs than in patients who have loss-of-function mutations in the genes for relevant transport proteins. In Gitelman’s syndrome the volume depletion, metabolic alkalosis, and stimulation of aldosterone secretion are less severe than in antenatal or classic Bartter’s syndrome. The effect of hypokalemia may predominate in this disorder and thus may explain the profound magnesium wasting that is a cardinal feature of Gitelman’s syndrome.

**MUTATIONS AFFECTING AN EXTRACELLULAR CALCIUM-SENSING RECEPTOR**

In 1972 a syndrome of “familial benign hypercalce mia” was described in 11 members of a large family. Hypocalciuria was also noted, and therefore this condition is also known as familial hypocalciuric hypercalcemia. The patients had mild hypermagnesemia as well; their serum parathyroid hormone concentrations were normal or mildly elevated. Calcium-infusion studies revealed a higher-than-usual set point for the release of parathyroid hormone in these patients,
Although the persistence of hypercalcemia and hypocalciuria after parathyroidectomy indicated that hyperparathyroidism was not the primary physiologic disturbance, and that the set point for renal calcium sensing might also be altered. In some infants born to consanguineous parents with familial hypercalcemic hyperparathyroidism, characterized by hypercalcemia, failure to thrive, osteopenia, and multiple fractures, develops soon after birth. Neutrophils, and multiple fractures, develops soon after birth. Cloning studies identified the extracellular calcium-sensing receptor, which is a G-protein–coupled receptor of 1078 amino acids. In the kidney, the calcium-sensing receptor is expressed on the basolateral surface of cells of the thick ascending limb, on the luminal surface of cells of the papillary collecting duct, and in other segments of the nephron. These are the sites at which hypercalcemia is known to inhibit reabsorption of sodium chloride, calcium, and magnesium in the thick ascending limb (Fig. 3) and to inhibit the hydro-osmotic effect of vasopressin in the collecting duct. Genetic-linkage studies mapped the gene for familial hypocalciuric hyperparathyroidism to the same region of chromosome 3 as the gene for the calcium-sensing receptor, strengthening the evidence of a potential role of this gene as the cause of familial hypocalciuric hyperparathyroidism and neonatal severe hyperparathyroidism. Mutations in the gene for the calcium-sensing receptor were soon documented, and over two dozen different mutations have now been identified in patients with these conditions.

Approximately two thirds of the studied kindreds with familial hypocalciuric hyperparathyroidism have had unique heterozygous mutations of the calcium-sensing receptor. These mutations cause the calcium-sensing receptor to respond only to higher-than-normal calcium concentrations, corresponding to a rightward shift in the set point for calcium-dependent responses. Neonatal severe hyperparathyroidism is usually caused by homozygous mutations in the children of consanguineous parents with hypocalciuric hyperparathyroidism, but a few patients have had new heterozygous mutations.

Gain-of-function mutations of the gene for the calcium-sensing receptor cause hypocalciuria with normal serum parathyroid hormone concentrations, a combination that suggests an abnormality in the set point of the calcium-sensing receptor. Expression studies confirmed that these mutations cause the receptor to respond to lower-than-normal concentrations of calcium, corresponding to a leftward shift in the dose–response curve for calcium-dependent responses. Patients with these mutations also have hypercalciuria, and some have nephrolithiasis and renal impairment, raising the possibility that abnormalities of the calcium-sensing receptor may contribute to idiopathic hypercalciuria.

**Mutations Affecting a Voltage-Gated Chloride Channel**

In the past several decades syndromes have been described that are characterized by various combinations of renal proximal tubular dysfunction, proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, renal failure, and rickets; these disorders have been referred to as Dent’s disease, X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and low-molecular-weight proteinuria with nephrocalcinosis. Their relation to each other was made clear by the recent demonstration that all are caused by mutations affecting a chloride channel. The spectrum of phenotypic features was remarkably similar in the various syndromes, except for differences in the severity of bone deformities and renal impairment. For example, in Japan a nationwide screening program for low-molecular-weight proteinuria led to the identification of very mild cases of this disease in asymptomatic schoolchildren. These X-linked syndromes should be viewed as variants of one disease that for simplicity’s sake can be called Dent’s disease, acknowledging Charles Dent, who in 1964 described two unrelated boys with hypercalciuric rickets and proximal tubular dysfunction.

Urinary loss of low-molecular-weight proteins is the most consistent abnormality: it is present in all affected males and in almost all female carriers of the disorder. Other signs of impaired solute reabsorption in the proximal tubule, such as renal glycosuria, aminoaciduria, and phosphate wasting, are variable and can be intermittent. Hypercalciuria is an early and common feature. Hypokalemia occurs in some patients. Urinary acidification is normal in over 80 percent of patients, and when it is abnormal, the defect has been attributed to hypercalciuria or nephrocalcinosis. The disease apparently does not recur after kidney transplantation.

These phenotypic features indicate the presence of proximal tubular dysfunction but do not suggest its pathophysiologic basis. However, mapping studies have established linkage to the short arm of the X chromosome (Xp11.22). A chromosomal microdeletion detected in one family led to mapping of the region and identification of a gene encoding a voltage-dependent chloride channel, CIC-5, that is expressed predominantly in the kidney. A total of 35 mutations have been identified to date in 46 families. Expression studies confirm that these mutations inactivate the chloride channel. Thus, positional cloning led to the identification of a disease-causing gene whose physiologic function was unknown. The gene is a member of a family of genes encoding voltage-gated chloride channels. These genes include CIC-I, the gene for the principal muscle chloride channel, which is mutated in Thomsen’s and Becker’s myotonias, and CIC-Kb, one of the genes responsible for Bartter’s syndrome (Fig.
3D). ClC-5 is expressed in the subapical endosomes of the proximal tubule, where it may allow chloride to enter the endosome and dissipate the positive charge generated during acidification by the proton ATPase. Impairment of this channel could limit endosomal acidification, thus causing defective reabsorption of proteins, and might also lead to impaired reabsorption of other solutes if membrane protein recycling were altered.

It is not clear how this process could explain the increased intestinal calcium absorption and high serum concentrations of 1,25-dihydroxyvitamin D in this disorder, because the 1α-hydroxylase that catalyzes its formation from 25-hydroxyvitamin D is located in the mitochondria of proximal tubular cells. ClC-5 is expressed in the thick ascending limb of Henle’s loop, which is a major site of renal calcium reabsorption. The role of this channel in the reabsorption of calcium in the thick ascending limb remains to be established. Expression of ClC-5 has also been reported in the acid-secreting α-intercalated cells of the collecting duct. The clinical or physiologic importance of this observation is uncertain, because the majority of patients with Dent’s disease have normal urinary acidification. However, in one pedigree, the initial description of the phenotype was “hereditary distal renal tubular acidosis.”

**Mutations Associated with X-Linked Hypophosphatemic Rickets**

Albright et al. recognized that in some patients with rickets, the disease did not respond to normal doses of vitamin D but did respond to large doses. They called this condition “vitamin D–resistant rickets.” The most common form of this condition is associated with hypophosphatemia, and its inheritance is X-linked. The hypophosphatemia is associated with a low threshold for renal tubular phosphate reabsorption, with increased urinary phosphate excretion. Defective proximal tubular reabsorption of phosphate in X-linked hypophosphatemic rickets would be expected to stimulate the production of 1,25-dihydroxyvitamin D, and yet serum 1,25-dihydroxyvitamin D concentrations are normal. As a consequence, urinary excretion of calcium is not increased and may even be reduced. Thus, the disease may involve defective regulation of the renal 1α-hydroxylase, in addition to defective sodium-dependent phosphate transport in the proximal tubule.

X-linked hypophosphatemic rickets was mapped to the short arm of the X chromosome at Xp22.1, and this led to the isolation of a gene that was mutated in patients with X-linked hypophosphatemic rickets. This gene encodes a protein that shares homologies with endothelin-converting enzyme, the Kell antigen, and a neutral endopeptidase. The gene is therefore referred to as *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome). The gene product is a type II integral membrane glycoprotein that has endopeptidase activity. In humans this protein is expressed in kidney, bone, and other tissues. Neutral endopeptidase and endothelin-converting enzyme are involved in the inactivation and activation of hormones, respectively. The physiologic function of the PHEX protein may be to activate a hormone that promotes phosphate retention or inactivate a phosphaturic hormone. Evidence of the existence of a phosphate-regulating hormone called “phosphatonin” is based largely on studies of patients with mesenchymal tumors who have hypophosphatemic osteomalacia (oncogenic osteomalacia). These patients have metabolic abnormalities that are indistinguishable from those in patients with X-linked hypophosphatemic rickets. Resection of the tumor, which is usually benign, corrects the metabolic abnormalities.

A related phenotype, hereditary hypophosphatemic rickets with hypercalciuria, differs from X-linked hypophosphatemic rickets in that affected patients have high serum 1,25-dihydroxyvitamin D concentrations, as would be expected if defective phosphate reabsorption was the only abnormality and 1α-hydroxylation of vitamin D was normally responsive to cellular phosphate depletion. Thus, unlike patients with X-linked hypophosphatemic rickets, these patients have increased intestinal absorption of calcium and hypercalciuria. The inheritance in the Bedouin kindred in which the disease was identified, in which there was a high degree of consanguinity, appeared to be autosomal recessive, and thus it seems unlikely that the X-linked genes *PHEX* and *ClC-5* are involved. The underlying defect could represent a loss of function of the sodium-dependent renal phosphate transporter in the apical membrane, which is encoded on chromosome 5. The characteristics of heterozygous females with this disorder resemble those of patients with idiopathic hypercalciuria, and thus the nature of the molecular defect in this disease may be relevant to the understanding of idiopathic hypercalciuria.

**Conclusions**

Each of the syndromes reviewed demonstrates the power of molecular and genetic techniques in defining the underlying pathophysiology of human disease. The candidate-gene approach was directly applied in the example of Liddle’s syndrome and pseudohypoaldosteronism type I. Dent’s disease and X-linked hypophosphatemic rickets provide contrasting examples in which genetic-linkage studies identified previously unknown candidate genes and thereby illuminated the physiologic role of newly described proteins. Studies of Barter’s and Gitelman’s syndromes demonstrate that phenotypic variations may be attributed to different genetic loci, all of which code for proteins that participate in an integrated
physiologic process (i.e., the reabsorption of sodium chloride in the thick ascending limb and distal convoluted tubule). Future advances may include the identification of additional genes to explain genetic heterogeneity, as occurs in Bartter’s syndrome, as well as the identification of genes that modulate phenotypic heterogeneity in the variable phenotype in Dent’s disease, for example. Polymorphisms in the genes for the transporters that have less severe functional consequences may explain more common transport disorders, such as idiopathic hypercalciuria, diuretic-induced renal potassium wasting, and even some forms of low-renin hypertension.

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