Title: Inherited tubulopathies of the kidney: insights from genetics

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*Abstract*
The kidney tubules provide homeostasis by maintaining the external milieu that is critical for proper cellular function. Without homeostasis, there would be no heartbeat, no muscle movement, no thought, sensation or emotion. The task is achieved by an orchestra of proteins, directly or indirectly involved in the tubular transport of water and solutes. Inherited tubulopathies are characterized by impaired function of one or more of these specific transport molecules. The clinical consequences can range from isolated alterations in the concentration of specific solutes in blood or urine to serious and life-threatening disorders of homeostasis. In this review, we will focus on genetic aspects of the tubulopathies and how genetic investigations and kidney physiology have cross-fertilized each other and facilitated the identification of these disorders and their molecular basis. In turn, clinical investigations of genetically defined patients have shaped our understanding of kidney physiology.

*Introduction*

Homeostasis refers to the maintenance of the “milieu interieur”, which, as expressed by the physiologist Claude Bernard is a “condition for a free and independent existence”.[1] Simplified, homeostasis with regards to the kidney follows the principle of balance: “what comes in, must come out”. Our bodies must maintain balance of fluids, electrolytes and acid-base despite great fluctuations from diet, metabolism and environmental conditions. If laboring in high temperatures with limited fluid intake, water must be preserved; if the diet contains a high acid load, this needs to be excreted and so on: the kidneys will adjust excretion of fluid and solutes, so that the total body balance is preserved. Specifically, it is the kidney tubules that perform this critical task, by adjusting reabsorption and secretion so that the final urine volume and composition matches the diet and environmental stressors. A whole array of transport proteins in the tubular epithelial cells is involved in this and their importance becomes most apparent, when one or more of them are defective. Collectively, these disorders are called kidney tubulopathies and a list of these is compiled in Table 1. The clinical consequences reflect the role of the affected transport protein: it can be isolated loss of specific solutes, which may even be of clinical benefit, considering for instance isolated renal glycosuria due to mutations in the sodium-glucose co-transporter type II, SGLT2. But they can also be devastating, if global homeostasis is affected, impairing even the most basic physiologic functions, such as respiration.[2]

Kidney physiologists often study genetically modified animals to better understand

the role of the respective gene. In contrast, clinicians studying patients with suspected tubulopathies find clues as to the potentially underlying cause through clinical observations. It is clinicians, who, together with genetic and physiologic scientists have often led the discovery of these transport molecules and their encoding genes and thereby provided fundamental insights into kidney physiology. In this review, rather than providing an exhaustive discussion of all tubulopathies, we will focus on the contribution of genetics to our current understanding of tubulopathies and, in turn, of kidney physiology.

*The Central Role of Salt*

On average, the human adult kidney filters approximately 150-180L of water and 20-25 mol of sodium per day, of which typically >99% is then reabsorbed back into the circulation by multiple sodium transport systems along the nephron (Figure 1).[3] The engine that drives tubular transport is the $Na^+$-$K^+$-ATPase, located on the basolateral aspect of the tubular epithelial cells. The stoichiometry of 3 sodium versus 2 potassium ion counter transport in concert with a potassium conductance establishes the crucial electrochemical gradient that facilitates sodium entry from the tubular lumen. Consequently, this gradient is used for the transport of many other solutes, such as glucose, various amino acids and phosphate (by co-transport), protons and potassium (by exchange), or calcium and uric acid (by facilitated diffusion).[3]

Genetic and clinical investigations into rare disorders of kidney salt handling have facilitated the cloning of many of the most important salt transport systems. Often this was in parallel with kidney physiologic studies. The identification of the

genetic basis of Bartter and Gitelman syndromes for instance fit perfectly with the understanding of kidney physiology and the clinical experience from loop and thiazide diuretics.[4] But in some instances, genetic investigations also provided very surprising results that prompted a revision of our understanding of physiology.

A key insight from these genetic studies is the recognition of kidney salt handling at the centre of blood pressure regulation and thus volume homeostasis.[5] Guyton described in the 1970's in detail the numerous physiologic processes implicated in affecting blood pressure and beautifully illustrated the integration of all these factors in a famous diagram.[6] But subsequent genetic studies of rare disorders associated with abnormal blood pressure clearly established kidney salt handling at the centre of long-term blood pressure regulation.[5]

An interesting observation from these disorders is the evolutionary ranking of the various aspects of homeostasis. Because the transport of many solutes in the tubule is directly or indirectly linked to sodium, this can create conflicts: for instance, in the collecting duct, the reabsorption of sodium via ENaC creates the favourable electrical gradient for the secretion of potassium and protons (Figure 1). Consequently, the biochemical "fingerprint" of enhanced sodium reabsorption in this segment is hypokalaemic alkalosis.[7] In Bartter and Gitelman syndromes, the kidneys excrete potassium and protons to facilitate sodium reabsorption, demonstrating the precedence of volume homeostasis over potassium and acid-base balance.[3] It follows naturally from this insight that salt supplementation should be beneficial also for normalizing plasma potassium levels in these salt wasting syndromes.[8]

Genetic investigations have also revealed how evolution has devised mechanisms to cope with competing homeostatic demands. The identification of the genetic basis of Pseudohypoaldosteronism type 2 (Gordon syndrome), elegantly solved the “aldosterone paradox”, the question of how aldosterone could be involved in the potentially conflicting demands of volume and potassium homeostasis.[9] If both sodium and potassium need to be preserved, sodium reabsorption is shifted to the DCT; if sodium must be preserved, but potassium excreted, for instance after a salt-poor, potassium-rich meal typical for the paleolithic diet, then sodium reabsorption is shifted to the collecting duct, facilitating potassium secretion.[9] These and other disorders also revealed the potassium sensing role of KCNJ10, the basolateral potassium channel in the DCT, mutations in which cause EAST syndrome.[10, 11] From a clinical perspective, this has important implications, as it explains why a high potassium intake facilitates excretion of the high salt content of a typical Western diet, thus mitigating the associated cardiovascular complications.[12]

Genetic studies have also revealed the sometimes haphazard nature of evolution. Intelligent design would likely have made the various steroid hormones specific for their respective receptors. Yet, the mineralocorticoid receptor is highly sensitive to the glucocorticoid cortisol, which is present in plasma in almost 1000-fold higher concentration than aldosterone.[13] Fortunately, specificity is provided by the enzyme HSD11B2, which metabolises cortisol to cortisone and thereby protects the mineralocorticoid receptor. Mutations in this enzyme lead to the rare hypertensive disorder of apparent mineralocorticoid excess.[13] The study of this

disorder also illustrates the importance of a comprehensive clinical investigation for a correct diagnosis, as this disorder shares many clinical features with Bartter syndromes types 1 and 2: hypokalemic alkalosis, hypercalciuria, and commonly secondary nephrogenic diabetes insipidus.[14] Only blood pressure and hormone levels can distinguish one disorder from the other: in apparent mineralocorticoid excess, blood pressure is elevated and aldosterone/renin levels are suppressed, while in the Bartter syndromes, the opposite is true.

Approximately 65% of sodium reabsorption occurs in the proximal tubule and experiments in mice show that the bulk of this occurs via the sodium-proton exchanger Nhe3.[15] Consequently, loss-of-function of NHE3 in humans was expected to be either incompatible with life, or at least lead to a severe form of proximal tubular acidosis.[16] Yet, when such loss-of-function mutations were identified, they were associated with the intestinal disorder congenital secretory sodium diarrhoea with no apparent kidney phenotype.[17] Further studies in mice demonstrated that a kidney-specific knock-out of Nhe3 does exhibit some bicarbonate-wasting, albeit mild.[18] Potentially, downstream isoforms of NHE provide compensation for NHE3-specific dysfunction in the proximal tubule, thereby explaining the mild kidney phenotype.

*Disorders of water*

Disorders of kidney water handling were amongst the first tubulopathies to be genetically solved, perhaps because of the typical clinical presentation: impaired kidney water conservation (nephrogenic diabetes insipidus) is associated with hypernatraemic dehydration, whereas impaired water excretion (nephrogenic syndrome of inappropriate antidiuresis) is associated with hyponatraemia.[19, 20]

Primary nephrogenic diabetes insipidus is associated with mutations in two genes, *AVPR2* and *AQP2*, encoding for the type 2 Arginine-Vasopressin (AVP) receptor and a water channel respectively (Figure 2).[21, 22] Detailed clinical observations in affected patients have revealed also extrarenal roles of AVPR2, expressed in the vasculature, where activation of the receptor results in vasodilatation and release of coagulation factors.[23]

Nephrogenic syndrome of inappropriate antidiuresis is characterised by an inability to dilute the urine, with a consequent risk of hyponatraemia from water overload.[20, 24]. It is thus the mirror image of nephrogenic diabetes insipidus: while nephrogenic diabetes insipidus reflects loss-of-function in the urinary concentration pathway, nephrogenic syndrome of inappropriate antidiuresis is caused by gain-of-function mutations in AVPR2.[20] Yet, no corresponding gain-of-function mutations in AQP2 have so far been described. Instead, mutations in *GNAS* have been identified as another cause of nephrogenic syndrome of inappropriate antidiuresis, either isolated or as part of a more complex syndrome, which reflects the association of GNAS with several G-protein coupled receptors.[25, 26] *GNAS* encodes the stimulatory G-α protein, which links AVPR2 activation to adenyl cyclase in the AVP signalling pathway (Figure 2).[27] Why some *GNAS* mutations lead to syndromic

features, whereas others seem to cause isolated nephrogenic syndrome of inappropriate antidiuresis is currently unclear. It has been speculated that AVPR2 signalling may be the most sensitive GNAS-associated pathway, so that milder mutation manifest clinically only in impaired urinary dilution.[25]

These disorders therefore provide important clinical insights, corresponding to those from salt handling disorders: whereas impaired kidney water handling is reflected in dysnatraemia, disorders of kidney sodium handling primarily result in altered volume homeostasis.

Moreover, they demonstrate the precedence of volume homeostasis over maintenance of normal plasma tonicity: in hypernatraemic dehydration in nephrogenic diabetes insipidus, the kidneys will preserve sodium, whereas in hyponatraemia water overload in the nephrogenic syndrome of inappropriate antidiuresis, sodium is excreted. Such insight informs also the diagnosis and treatment of the more common, but related disorder, the syndrome of inappropriate anti-diuresis (SIADH), which due to its elevated urinary sodium concentration is commonly misdiagnosed as cerebral or pulmonary salt wasting.[7] Treatment with salt supplementation thus just re-establishes the volume overload and consequently risks hypertension. Instead, asymptomatic SIADH should be treated by water removal.[28]

*Acid-base homeostasis*

Early clinical and physiological investigations distinguished renal tubular acidosis (RTA) into a proximal and distal form, to which a mixed form was later added.[29, 30]

Subsequent discovery of the underlying genes beautifully confirmed the initial astute clinical observations as these genes encoded proteins involved in either proximal bicarbonate reabsorption (proximal RTA) or distal proton secretion (distal RTA) or both (Figure 3). Proximal RTA typically occurs in subjects with generalised proximal tubular dysfunction (Fanconi renotubular syndrome). Isolated proximal RTA is exceedingly rare, associated also with eye abnormalities and due to mutations in the basolateral sodium/bicarbonate exchanger SLC4A4.[31] A further family with apparently isolated proximal RTA and dominant inheritance has been described, but the genetic basis remains so far unsolved.[32] SLC9A3 (see above) was considered a strong candidate, but this could not be confirmed, illustrating how our understanding of kidney physiology, derived mainly from animal models, can at times be critically informed by insights from human genetics.[16]

Genetic investigations into distal renal tubular acidosis, provided insights into the different functions of the chloride/bicarbonate anion exchanger AE1. This transport protein, encoded by *SLC4A1* and initially identified in Western blots from red cells ("Band 3") was already associated with East-Asian ovalocytosis and hereditary spherocytosis, but subsequently found to also cause distal RTA.[33]

Physiologic investigations have highlighted the role of both the $H^+$-ATPase and $H^+/K^+$-ATPase in the collecting duct for distal acid secretion.[34, 35] Yet, so far only in 2 of the 14 different subunits of the $H^+$-ATPase have mutations been identified (ATP6V0A4 and ATP6V1B1) that cause distal RTA and in none of the $H^+/K^+$-ATPase.[36, 37] The remaining genes are obviously strong candidate genes for the 30-40% of genetically unsolved patients with a clinical diagnosis of primary distal

RTA, yet so far no convincing mutations have been reported.[38] Instead, 2 different genes have emerged as novel distal RTA disease genes: the first one, *FOXI1*, fits perfectly with current understanding of physiology.[39] It encodes a transcription factor regulating the expression of several proteins involved in acid secretion and mice deleted for the murine paralogue had been previously described to have distal RTA.[40] Mutations in transcription factors are usually inherited in a dominant fashion, probably reflecting the fact that complete loss is not compatible with life.[41] The fact that *FOXI1* mutations are recessively inherited highlights the specific and restricted role of this transcription factor in acid secreting epithelia.

In contrast to *FOXI1*, the discovery of *WDR72* as a distal RTA disease gene was completely unexpected, illustrating the power of genetics to provide novel insights.[42] Mutations in *WDR72* were identified in several patients with a syndromic combination of amelogenesis imperfecta and distal RTA. The exact mechanisms of how *WDR72* mutations are linked to distal RTA remain unclear at present. Interestingly, WDR72 mutations had been previously identified as a cause of amelogenesis imperfecta.[43] Whether some mutations cause isolated dental problems, others distal RTA or both, or whether the dentist may have missed distal RTA, just as the nephrologist may have missed amelogenesis imperfecta remains unclear. Interestingly, the identification of WDR72 mutations in a cohort of distal RTA patients led to the subsequent diagnosis of amelogenesis imperfecta in all affected patients by “reverse phenotyping”.[44] This is reminiscent of the identification of *FAM20A* mutations first as a cause of amelogenesis imperfecta and subsequently also of nephrocalcinosis[45]. Arguably, these examples illustrate

the narrow clinical focus of individual medical specialties and the importance of comprehensive phenotyping.

Clinical studies in subjects with acid-base abnormalities reveal the critical importance of precise acid-base balance for proper physiological function of our body, reflected in the exquisitely tight control of arterial pH between 7.37 and 7.43, a change of less than ±3 nmol/l. Protons can bind to proteins, especially to histidine residues and thereby affect protein charge, which in turn affects protein-folding and function. Consequently, disturbances of acid-base balance are potentially catastrophic and can include dysrhythmias, apnoea, coma and death.[46] And even relatively mild forms of distal RTA reveal that acidosis is associated not only with rickets and nephrocalcinosis/urolithiasis but also with more general symptoms, such as impaired growth.[47]

*Magnesium homeostasis*

Magnesium (Mg) is the second most abundant intracellular cation and a cofactor in numerous enzymatic reactions, yet it is often called the "forgotten ion".[48] Magnesium homeostasis is primarily maintained though reabsorption in the TAL and DCT and clinically, this can be typically distinguished by the concurrence of hypercalciuria (TAL) or normo-/hypocalciuria (DCT).[49] All known genetic causes of hypomagnesemia encode proteins expressed in these functional segments of the nephron (Figure 4). In the TAL, calcium and magnesium are reabsorbed through a common paracellular pathway, lined by CLDN16 and CLDN19, mutations in

which cause hypercalciuric hypomagnesaemia.[49] Interestingly, mutations in CLDN10, another claudin that lines this paracellular pore, enhance magnesium reabsorption and thereby cause hypermagnesaemia as part of a more complex phenotype called HELIX syndrome.[50]

Even though paracellular reabsorption of cations depends on a transepithelial voltage gradient, which is established by the combined function of NKCC2 and ROMK1, the corresponding recessive disorders Bartter syndromes type 1 and 2 are usually not associated with hypomagnesaemia.[3] In contrast, dominant gain-of-function mutations in the calcium-sensing receptor which suppress ROMK function do associate with hypomagnesaemia, likely because of other functional roles of this receptor.[49]

While only about 10% of filtered magnesium is reabsorbed in the DCT this represents the final regulated pathway and genetic investigations have revealed a surprising complexity: at least 15 genes have so far been identified, mutations in which impair magnesium transport in this segment (Table 1 and Figure 4). These are associated with hypocalciuria, if not only magnesium but also salt reabsorption is affected ("Gitelman-like" hypomagnesaemias[49]), as the resulting hypovolaemia leads to increased proximal sodium and thus calcium reabsorption.[51] In contrast, disorders affecting magnesium transport only are associated with normocalciuria. The most prominent example for the latter is Familial Hypomagnesaemia with secondary Hypocalcaemia and the identification of the underlying genetic basis as mutations in TRPM6 established this channel as the key magnesium transport pathway in the apical membrane of the DCT.[52]

There are some interesting observations in genetically defined patients with hypomagnesaemia. For instance, mutations impairing the function of the basolateral $Na^+$-$K^+$-ATPase primarily seem to predominantly affect magnesium transport. Mutations in the alpha (ATP1A1)[53] or gamma (FXYD2)[54] subunit, or in their regulators, such as HNF1B[55] manifest primarily with hypomagnesaemia, even though a trend to a Gitelman-like tubulopathy may be observed.[56] Presumably, this reflects the critical role of the DCT for magnesium homeostasis, whereas other segments may be able to compensate more with regards to sodium.[57]

Another interesting observation is the apparent absence of hypokalaemia in patients with TRPM6 mutations.[58] Because ROMK is inhibited by intracellular magnesium, hypomagnesaemia has been proposed as a cause for refractory hypokalaemia.[59] Yet, these patients, despite their often profound hypomagnesaemia, are not reported to suffer from hypokalaemia, seriously questioning the clinical relevance of hypomagnesaemia for potassium control.

A relevant physiological question arising from the genetic findings in patients with hypomagnesaemia is regarding the link between impaired sodium transport in DCT and magnesium reabsorption. Presumably, apical sodium uptake via SCL12A3 is necessary to maintain the activity of the $Na^+$-$K^+$-ATPase, which in turn establishes the electrochemical gradient that facilitates magnesium uptake. To do so, an apical potassium channel is needed that can translate this electrochemical gradient into a lumen-negative membrane potential to enable magnesium uptake via TRPM6. The identification of a familial form of hypomagnesaemia associated with a mutation in the apically expressed potassium channel KCNA1 fits nicely with this

hypothesis, except that this is a voltage-gated potassium channel with essentially zero open probability at the membrane voltages observed in DCT.[60] Moreover, other mutations in KCNA1 are the cause of episodic ataxia type 1, which is not associated with hypomagnesaemia.[49] Further studies are needed to resolve these apparent conundrums.

Genetic investigations have also provided some insights with regards to the identity of the basolateral transport pathway for magnesium in DCT, although questions remain. Initially, CNNM2 was thought to constitute this pathway in the form of a basolateral sodium-magnesium exchanger, but later it was also proposed to be an intracellular magnesium sensor.[61, 62] Thus, whether CNNM2 constitutes the main basolateral exit pathway, or whether other transport proteins are involved remains currently unclear.

*Genetic testing in tubulopathies*

Currently, more than 50 disease genes for kidney tubulopathies are recognized (Table 1) and the list keeps on expanding. Due to the specific phenotype associated with mutations in most genes, an accurate clinical diagnosis can usually be established. However, even in expert centres, genetic testing can sometimes further specify or even correct the clinical diagnosis, so that genetic confirmation is usually recommended, because of potentially important implications not only for genetic counselling, but also for treatment.[63, 64] For instance, Bartter syndrome is occasionally misdiagnosed as nephrogenic diabetes insipidus and the common therapeutic use of thiazides for the latter could have life

threatening consequences in the former disorder.[27] Whether genetic testing is done by sequencing of single genes, a targeted panel or whole exome/genome depends on the certainty of the clinical diagnosis and local availability/affordability. If no causative variant(s) are identified by selected gene sequencing, a subsequent more comprehensive approach is necessary to reach a genetic diagnosis. For this reason, whole exome/genome sequencing is increasingly used as a first line approach. In the UK for instance, the aim is to use whole genome sequencing for the vast majority of genetic tests (https://www.england.nhs.uk/genomics/nhs-genomic-med-service/). In order to minimize the analytical workload and the risk of incidental findings, only a panel of relevant disease genes is assessed. Obviously, these gene panels need to be constantly updated and various resources for this exist.[65]

Yet, while the diagnostic yield of genetic testing in tubulopathies is much higher than in most other kidney disorders, in about a third of patients with paediatric onset tubulopathy, a genetic diagnosis cannot be established and this increases to more than two thirds in those with adult onset.[63, 64] This likely reflects the diagnostic uncertainty regarding some identified variants, or genes, as well as acquired causes, especially in adult onset patients.

*Translation of genetic insights*

Genetic investigations have provided unparalleled insights into the molecular basis of tubular physiology and thus the maintenance of homeostasis. While discoveries of new Mendelian disease genes are still ongoing, their number is necessarily

limited. Other genetic approaches, such as genome-wide association studies may provide further insights into the genetic architecture of tubulopathies and the maintenance of homeostasis.[66]

Translating genetic discoveries into targeted treatments is an obvious key aim. Many of the identified molecular causes were already known as targets of drugs, such as diuretics. For disorders with a gain-of-function disease mechanism, treatment can be logical and targeted, such as the use of thiazides in Pseudohypoaldosteronism type 2 or amiloride in Liddle syndrome. In some instances, understanding of the molecular mechanism has provided a basis for the development of a specific treatment. One that has now entered the clinical arena is the anti-FGF23 antibody Burosumab in X-linked hypophosphataemic rickets.[67] Another example is the recognition of the central role of cyclic adenosine monophosphate in kidney water handling, which has spurned investigations into novel treatments for nephrogenic diabetes that enhance AQP2 expression in the apical membrane independent of AVPR2 receptor activation.[68-70]

Yet, for most tubulopathies treatment has remained essentially unchanged over the past decades and is mainly supportive, for instance in the form of electrolyte supplements. Fortunately, the advent of gene editing technologies, such as CRISPR/CAS9 may provide opportunities for the future treatment of tubulopathies.[71] In contrast to most other genetic kidney disorders, such as inherited kidney malformations or nephronophthisis, in which global kidney architecture and function is typically irreversibly altered at the time of diagnosis, tubulopathies affect only very specific aspects of kidney function. While there may

be some irreversible changes, such as nephrocalcinosis or interstitial fibrosis, most patients with tubulopathies would have sufficient kidney function, if the genetic defect could be repaired.

A key obstacle remains the targeted delivery of the gene editing machinery to the kidney. So far, clinical trials of gene editing address mostly haematological or immune disorders, where relevant blood cells can be obtained for gene editing *ex vivo* and then returned to the patient (www.clinicaltrials.gov).[72] However, if precise delivery to the tubule can be achieved, then tubulopathies will constitute an ideal group of disorders for the therapeutic application of this promising new technology. Another approach currently trialed is delivery of the correct gene via hematopoietic stem cells.[73]

## Conclusions

Tubulopathies of the kidney illustrate the synergistic potential of clinical, genetic and physiological investigations to facilitate accurate diagnosis and targeted management of affected patients while in turn enhancing our understanding of kidney physiology. They reveal the central role of sodium in overall tubular transport, the primate of volume over other aspects of homeostasis and its control through sodium reabsorption. Tubulopathies also sometimes dramatically illustrate the critical importance of homeostasis for overall body function.

The high rate of identifiable underlying genetic causes and the fact that they affect

very specific aspects of tubular function, while generally preserving overall kidney function make them ideal targets for future treatments using gene editing techniques.

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Table 1: List of inherited tubulopathies

| | Inheritance | Gene | Protein | OMIM |
|---|---|---|---|---|
| **Proximal Tubule** | | | | |
| Fanconi Renotubular syndrome 1 | AD | *GATM* | L-ARGININE:GLYCINE AMIDINOTRANSFERASE | #134600 |
| Fanconi Renotubular syndrome 2 | AR | *SLC34A1* | NaPi2A | #182309 |
| Fanconi Renotubular syndrome 3 | AD | *EHHADH* | PBFE | #607037 |
| Fanconi Renotubular syndrome 4 | AD | *HNF4A* | HNF-4 | #600281 |
| Fanconi-Bickel Syndrome | AR | *SLC2A2* | GLUT-2 | #138160 |
| Dent Disease Type 1 | XLR | *CLCN5* | CLC-5 | #300008 |
| Dent Disease Type 2/Lowe Syndrome | XLR | *OCRL* | OCRL | #300535 |
| Renal Tubular Acidosis Type 3 | AR | *CA2* | Carbonic Anhydrase 2 | #611492 |
| Hereditary hypophosphatemic rickets with hypercalciuria | AR | *SLC34A3* | NaPi2c | #241530 |
| X-linked hypophosphatemic rickets | XLD | *PHEX* | PHEX | #307800 |
| Cystinuria A | AD | *SLC3A1* | rBAT | #104614 |
| Cystinuria B | AR | *SLC7A9* | b(0,+)AT1 | #604144 |
| Lysinuric protein intolerance | AR | *SLC7A7* | y(+)LAT1 | #222700 |
| Hartnup disorder | AR | *SLC6A19* | B(0)AT1 | #234500 |
| Iminoglycinuria | AR/Digenic | *SLC36A2+SLC6A20/SLC6A19* | SLC36A2+SLC6A20/SLC6A19 | #242600 |
| Dicarboxylic Aminoaciduria | AR | *SLC1A1* | ? | #222730 |
| **Thick Ascending Limb** | | | | |
| Bartter Type 1 | AR | *SLC12A1* | NKCC2 | #600839 |
| Bartter Type 2 | AR | *KCNJ1* | ROMK | #600359 |
| Bartter Type 3 | AR | *CLCNKB* | CLC-Kb | #602023 |
| Bartter Type 4a | AR | *BSND* | Barttin | #606412 |
| Bartter Type 4b | Digenic | *CLCNKA+CLCNKB* | CLC-Ka+CLC-Kb | #602024 |
| Bartter Type 5 | XR | *MAGED2* | MAGED2 | #601199 |

| | | | | |
|---|---|---|---|---|
| Hypomagnesaemia type 3 / Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis | AR | *CLDN16* | Claudin16 | #603959 |
| Hypomagnesaemia type 5 / Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis | AR | *CLDN19* | Claudin19 | #610036 |
| Autosomal dominant hypocalcaemia | AD | *CaSR* | Calcium sensing receptor | #601198 |
| Kenny−Chaffey syndrome type 2 | AD | *FAM111A* | FAM111A | #127000 |
| | | | | |
| **Distal Convoluted Tubule** | | | | |
| Gitelman Syndrome | AR | *SLC12A3* | NCCT | #600968 |
| EAST/SeSAME Syndrome | AR | *KCNJ10* | Kir4.1 | #602028 |
| Pseudohypoaldosteronism Type 2b | AD | *WNK4* | WNK4 | #601844 |
| Pseudohypoaldosteronism Type 2c | AD | *WNK1* | WNK1 | #605232 |
| Pseudohypoaldosteronism Type 2d | AD/AR | *KLHL3* | KLHL3 | #614495 |
| Pseudohypoaldosteronism Type 2e | AD | *CUL3* | CUL3 | #614496 |
| Hypomagnesaemia type 1 / Hypomagnesaemia with secondary hypocalcaemia | AR | *TRPM6* | TRPM6 | #607009 |
| Hypomagnesaemia type 2 | AD | *FXYD2* | Na-K-ATPase | #154020 |
| Autosomal dominant hypomagnesaemia | AD | *KCNA1* | Kv1.1 | #176260 |
| HNF1B-related kidney disease | AD | *HNF1B* | HNF1B | #137920 |
| | | | | |
| Hyperphenylalaninemia BH4-deficient | AR | *PCBD1* | PCDB1 | #264070 |
| Hypomagnesaemia type 4 | AR | *EGF* | EGF | #611718 |
| Neonatal inflammatory skin and bowel disease type 2 | AR | *EGFR* | EGFR | #616069 |
| Hypomagnesemia, seizures, and mental retardation type 1 | AD/AR | *CNNM2* | CNNM2 | #613882 |

| | | | | |
|---|---|---|---|---|
| Hypomagnesemia, seizures, and mental retardation type 2 | *de novo* | *ATP1A1* | ATP1A1 | #618314 |
| **Collecting Duct** | | | | |
| Pseudohypoaldosteronism Type 1 | AR | SCNN1A | ENaC alpha subunit | #600228 |
| Pseudohypoaldosteronism Type 1 | AR | SCNN1B | ENaC beta subunit | #600760 |
| Pseudohypoaldosteronism Type 1 | AR | SCNN1G | ENaC gamma subunit | #600761 |
| Pseudohypoaldosteronism Type 1A | AD | NR3C2 | MR | #600983 |
| Liddle Syndrome | AD | SCNN1B | ENaC beta subunit | #600760 |
| Liddle Syndrome | AD | SCNN1G | ENaC gamma subunit | #600761 |
| Apparent mineralocorticoid excess | AR | *HSD11B2* | 11-β-HSD2 | #614232 |
| Glucocorticoid remediable aldosteronism | AD | *CYP11B1/CYP11B2* | 11-β-hydroxylase/ALDOS | #610613 |
| Congenital adrenal hyperplasia Type 1 | AR | *CYP21A2* | 21-hydroxylase | #613815 |
| Congenital adrenal hyperplasia Type 2 | AR | *HSD3B2* | 3-β-HSD2 | #613890 |
| Congenital adrenal hyperplasia Type 4 | AR | *CYP11B1* | 11-beta-hydroxylase | #610613 |
| Congenital adrenal hyperplasia Type 5 | AR | *CYP17A1* | 17-α-hydroxilase | #609300 |
| Nephrogenic diabetes insipidus | XLR/ | *AVPR2* | AVPR2 | #300538 |
| Nephrogenic diabetes insipidus | AR/AD | *AQP2* | AQP-2 | #107777 |
| Nephrogenic syndrome of inappropriate antidiuresis | XLR | *AVPR2* | V2R | #300538 |
| Nephrogenic syndrome of inappropriate antidiuresis | AD | *GNAS* | G-alpha s | |
| distal RTA | AD/AR | *SLC4A1* | AE1 | #109270 |
| distal RTA | AR | *ATP6V1B1* | V-ATPase subunit B1 | #192132 |
| distal RTA | AR | ATP6V0A4 | V-ATPase subunit a4 | #605239 |
| distal RTA | AR | FOXI1 | Forkhead box protein I1 | #601093 |
| distal RTA | AR | WDR72 | WD repeat-containing protein 72 | #613214 |

Table 1: Listed are primary renal tubulopathies grouped by affected nephron segment, the underlying gene(s) and encoded protein(s), as well as their OMIM entry number.

RTA: renal tubular acidosis

Figure legends

Figure 1: Shown is an overview of a nephron, detailing selected transporters involved in disorders of tubular sodium handling. For associated disorders, please see table 1.

Figure 2: Shown is a schematic of a principal cell in the collecting duct (CD) with relevance to water transport. Note the expression of AVPR2 on the basolateral side. Activation of this receptor results in insertion of AQP2 into the apical membrane.

Figure 3: Shown is a schematic of a tubular epithelial cell in thick ascending limb of Henle's loop (TAL) and distal convoluted tubule (DCT), highlighting proteins involved in tubular magnesium handling.

Figure 4: Shown is a schematic of a tubular epithelial cell in PT and an intercalated cell (type A) in the collecting duct (CD), highlighting proteins involved in bicarbonate reabsorption and acid secretion.