Mechanisms of ion transport regulation by HNF1β in the kidney: beyond transcriptional regulation of channels and transporters

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Abstract
Hepatocyte nuclear factor 1β (HNF1β) is a transcription factor essential for the development and function of the kidney. Mutations in and deletions of HNF1β cause autosomal dominant tubule interstitial kidney disease (ADTKD) subtype HNF1β, which is characterized by renal cysts, diabetes, genital tract malformations, and neurodevelopmental disorders. Electrolyte disturbances including hypomagnesemia, hyperuricemia, and hypocalciuria are common in patients with ADTKD-HNF1β. Traditionally, these electrolyte disturbances have been attributed to HNF1β-mediated transcriptional regulation of gene networks involved in ion transport in the distal part of the nephron including FXYD2, CASR, KCNJ16, and FXR. In this review, we propose additional mechanisms that may contribute to the electrolyte disturbances observed in ADTKD-HNF1β patients. Firstly, kidney development is severely affected in Hnf1b-deficient mice. HNF1β is required for nephron segmentation, and the absence of the transcription factor results in rudimentary nephrons lacking mature proximal tubule, loop of Henle, and distal convoluted tubule cluster. In addition, HNF1β is proposed to be important for apical-basolateral polarity and tight junction integrity in the kidney. Interestingly, cilia formation is unaffected by Hnf1b defects in several models, despite the HNF1β-mediated transcriptional regulation of many ciliary genes. To what extent impaired nephron segmentation, apical-basolateral polarity, and cilia function contribute to electrolyte disturbances in HNF1β patients remains elusive. Systematic phenotyping of Hnf1b mouse models and the development of patient-specific kidney organoid models will be essential to advance future HNF1β research.

Keywords HNF1β · Electrolyte disturbances · Transcriptional regulation · Kidney development · Apical-basolateral polarity

Introduction
Hepatocyte nuclear factor 1β (HNF1β) is a transcription factor expressed in epithelial tissues including the kidney, pancreas, liver, and genital tract and is essential for the development and function of these tissues [20, 22, 32, 33, 45, 90]. Within the kidney, HNF1β is expressed in all epithelial cells of the nephron and operates in homodimeric or heterodimeric complexes with HNF1α [20].

Mutations or deletions in HNF1β are responsible for a dominantly inherited, multisystem disease called autosomal dominant tubulointerstitial kidney disease type HNF1β (ADTKD-HNF1β) [27]. The disease was originally described as renal cysts and diabetes syndrome (RCAD), as kidney cysts (present in 60% of all patients) and maturity-onset diabetes of the young (MODY5) (40%) are common in patients with HNF1β defects [79]. However, the disease has a variable presentation, and not all patients suffer from cysts or diabetes. Kidney anomalies are often present and include renal hypoplasia, unilateral renal agenesis, microcystic dysplasia, and horseshoe kidney. As a consequence, kidney function is impaired in approximately half of the affected children and adults and progresses to end-stage renal disease in 12% of the patients [28, 57, 65]. In contrast to other cystic disorders, electrolyte disturbances are common in ADTKD-HNF1β patients [29, 49, 65]. In particular, the presence of hypomagnesemia is an important predictive criterium to
suspect ADTKD-HNF1β [65]. Additionally, hypokalemia, hypocalciuria, hyperparathyroidism, and metabolic alkalosis are present in a minor group of patients [4, 10, 77, 79]. Extrarenal manifestations of ADTKD-HNF1β consist of diabetes, neurodevelopmental disorders, genital and urinary tract malformations, gout, and elevated liver enzymes [10, 12, 79].

The incidence of HNF1β defects is estimated to be 1:200,000 [91]. Approximately 150 different mutations have been reported [18]. These mutations can be familial with a dominant inheritance pattern (60%) or de novo (40%). The majority of the mutations are localized in the first four exons encoding the dimerization domain and DNA-binding domains, which are required for binding of HNF1β to the genomic sequence 5′-TTAATNTTTAAC-3′ in promoter or enhancer elements [18, 86]. In addition to intragenic mutations, a 17q12 deletion spanning 15 genes, including HNF1β, accounts for 50% of the cases [19, 26]. Consequently, it is essential to perform an analysis of structural variants in the HNF1β gene, for instance by multiplex ligation-dependent probe amplification (MLPA).

Several groups have attempted to formulate diagnostic criteria to select patients for genetic HNF1β screening. Faguer and colleagues created a HNF1β score based on the clinical presentation [29]. However, several groups demonstrated that patients can be missed using the HNF1β score due to the variability in clinical presentation [18, 65]. The current KDIGO guidelines, therefore, use much simpler diagnostic criteria mainly based on the presence of kidney anomalies [27]. However, these criteria are often not specific for the HNF1β subtype of ADTKD and bear the risk of not identifying the patients that initially present with diabetes or electrolyte phenotype [26, 77]. Several groups have demonstrated that the presence of hypomagnesemia may be particularly predictive of HNF1β mutations [6, 65, 77].

In this review, we present the current knowledge on the electrolyte disturbances in ADTKD-HNF1β patients and discuss the possible mechanisms underlying these disturbances.

Electrolyte disturbances in ADTKD-HNF1β patients

The introduction of next-generation sequencing in standard genetic diagnostic pipelines has resulted in the identification of thousands of ADTKD-HNF1β patients worldwide. Although ADTKD-HNF1β is a rare Mendelian disorder, these technological advances have allowed the formation of large cohorts of HNF1β patients [6, 26, 48, 55, 57]. Careful phenotyping of these cohorts has demonstrated that hypomagnesemia, hyperparathyroidism, hyperuricemia, and hypocalciuria are common in patients with HNF1β defects [5, 6, 30, 55, 92]. Only a minority of the patients have electrolyte disturbances including hypokalemia, metabolic alkalosis, and polyuria [6].

Hypomagnesemia (serum magnesium (Mg2+) < 0.7 mM) is the most common electrolyte disturbance in ADTKD-HNF1β patients. The penetrance of this symptom is estimated to range between 25 and 75% [5, 6, 29, 65, 77]. Several groups have aimed to explain the variability of reported hypomagnesemia cases among cohorts. Prospective cohort studies tend to report the presence of hypomagnesemia more often than retrospective analyses, indicating the poor implementation of Mg2+ measurements in the standard clinical blood biochemistry panels [77]. Several reports noted that young children have generally higher serum Mg2+ concentrations [6, 18, 77]. It was therefore proposed that hypomagnesemia developed later in childhood [6]. However, this notion was recently challenged by Kolbuc and colleagues [92]. Their detailed analysis demonstrated that serum Mg2+ levels are higher in early childhood in both HNF1β patients and healthy controls. Consequently, the reference range of 0.7–1.1 mmol/L is not applicable for young children, resulting in an underestimation of hypomagnesemia in early childhood. Studies establishing age- and gender-specific reference ranges are, therefore, needed.

Hyperparathyroidism (serum parathyroid hormone (PTH) > 6.5 pmol/L) was initially only described in single patients [5, 28]. However, systematic PTH measurements in small cohort studies demonstrated the presence of increased PTH levels in 80% of patients [30, 55]. Because PTH is not reported in many cohort studies, the exact percentage of ADTKD-HNF1β patients suffering from hyperparathyroidism is unknown. Especially, because small cohort studies tend to report the presence of hypomagnesemia more often than retrospective analyses, indicating the poor implementation of Mg2+ measurements in the standard clinical blood biochemistry panels [77]. Of note, chronic kidney disease may contribute to elevated PTH levels on top of direct HNF1β effects.

Hyperuricemia (serum uric acid > 8 mg/dL) is present in 20–30% of all patients with ADTKD-HNF1β [48, 55, 57, 65]. Reduced kidney function is considered the main mechanism explaining hyperuricemia in ADTKD-HNF1β. Additionally, serum uric acid is independently associated with PTH levels, suggesting that PTH contributes to the molecular mechanism [92]. Indeed, PTH is known to inhibit uric acid secretion by downregulation of ATP-binding cassette transporter G2 (ABCG2) [74]. Interestingly, HNF1β also regulates the expression of renal urate transporter URAT1 [39]. Nevertheless, hyperuricemia and hyperparathyroidism are poor predictors of HNF1β defects as it is also common in other forms of end-stage renal disease [65, 92].

Hypocalciuria is common in patients with ADTKD-HNF1β. The exact penetrance of hypocalciuria is unknown because the reference range for renal calcium (Ca2+) excretion has no generally established lower limit. Nevertheless, several studies demonstrated that urinary Ca2+ levels are...
significantly lower in patients with HNF1β defects compared to controls [5, 6].

Although serum potassium (K+) and bicarbonate (HCO₃⁻) levels are poorly reported in ADTKD-HNF1β cohorts, Adalat and colleagues demonstrated that HNF1β patients have decreased serum K+ and increased serum HCO₃⁻ levels, especially in late childhood [6]. Indeed, case reports have reported K+ values close to the lower border of the reference range (serum K+ 3.5–5.0 mM) [6, 28, 77]. Although these patients are not strictly hypokalemic, their serum K+ concentration is lower than in the general population.

The presence of hypomagnesemia, hypokalemia, metabolic alkalosis, and hypocalciuria is reminiscent of the phenotype of Gitelman syndrome [93, 94]. Indeed, the initial diagnosis of some patients has been Gitelman syndrome, until genetic investigations revealed mutations in the HNF1β gene [7]. However, it should be noted that renin–angiotensin–aldosterone system (RAAS) activation is scarce in patients with HNF1β defects, whereas it is a cardinal symptom of Gitelman patients. Moreover, hypertension is present in 22% of children with ADTKD-HNF1β, whereas Gitelman patients are generally hypotensive compared to healthy family members [69, 95]. Although it should be noted that chronic kidney disease in ADTKD-HNF1β patients may contribute to the hypertension phenotype.

Mechanisms of disturbed electrolyte transport in ADTKD-HNF1β patients

The disturbed electrolyte transport caused by defects in HNF1β has classically been attributed to direct transcriptional regulation of key transporter genes along the nephron [79, 96]. In this review, we will provide an overview of the main transport mechanisms that are determined by HNF1β function. Moreover, we will consider additional mechanisms beyond direct transcriptional regulation, which may contribute to the ADTKD-HNF1β disease phenotype.

Transcriptional control of transporters and channels

The hypomagnesemia, hypokalemia, and hypocalciuria observed in ADTKD-HNF1β patients are generally assigned to distal tubule dysfunction. In the first description of electrolyte defects in ADTKD-HNF1β patients by Adalat and colleagues, FXYD2 was identified as a transcriptional target in the distal convoluted tubule (DCT) (Fig. 1) [5]. FXYD2 encodes the γ subunit of the Na⁺-K⁺-ATPase, and FXYD2 mutations are causative for hypomagnesemia [23, 51]. In recent years, the cardinal role of the Na⁺-K⁺-ATPase was further demonstrated by the identification of ATP1A1 mutations, encoding the α subunit of the Na⁺-K⁺-ATPase, as a cause of hypomagnesemia [67]. It has been hypothesized that reduced Na⁺-K⁺-ATPase activity in the DCT will result in depolarization of the basolateral membrane, resulting in an increased intracellular chloride (Cl⁻) concentration. Indeed, a high intracellular Cl⁻ concentration has been established to inhibit WNK kinases and thereby the phosphorylation and activity of the thiazide-sensitive Na⁺-Cl⁻ co-transporter (NCC). Clinical studies confirmed that ADTKD-HNF1β patients have a diminished response to thiazide, confirming lower NCC activity in patients [8]. Interestingly, NCC expression is also decreased in Hnf1b knock-out (KO) mice [41].

Moreover, HNF1β regulates the transcription of KCNJ16, which codes for the Kir5.1 subunit of the basolateral K⁺ channel in the DCT (Fig. 1) [41]. This Kir4.1/Kir5.1 K⁺ channel allows recycling of K⁺ to drive Na⁺-K⁺-ATPase activity. Uncoupling of this “pump-leak mechanism” will result in depolarization of basolateral membrane activity and reduced NCC activity by the same mechanisms as described above [97]. The importance of the Kir4.1/Kir5.1 channel was further established by the identification of KCNJ10 and KCNJ16 mutations in patients with hypokalemia and hypomagnesemia, mimicking Gitelman syndrome [13, 68, 98]. Nevertheless, hypokalemia and metabolic alkalosis are only present in a subset of patients with HNF1β defects, which is in line with the phenotype of patients with FXYD2 or ATP1A1 mutations [23, 67]. One might hypothesize that this phenotypic variability is explained by the degree of Na⁺-K⁺-ATPase dysfunction and the presence of compensatory effects.

The concomitant HNF1β-dependent regulation of basolateral Na⁺ and K⁺ transport by FXYD2 and KCNJ16 demonstrates that transcription factors generally regulate gene networks rather than single genes. Similarly, HNF1β determines a gene network controlling the urine concentrating ability of the kidney [2]. A collecting duct-specific Hnf1b KO mouse model showed a reduced urine osmolality [2]. RNA sequencing and ChIP sequencing identified 27 osmosensitive genes that are dependent on HNF1β binding [2]. Among the HNF1β targets is the farnesoid X receptor (FXR), which is essential for urine concentration by regulating aquaporin 2 (AQP2) expression (Fig. 1) [2, 88]. Indeed, apical plasma membrane expression of AQP2 is reduced in collecting duct cells expressing an Hnf1b mutant [2]. Interestingly, FXR directly activates the expression of Mg²⁺ channel Trpm6 in mouse intestines [40]. Hence, HNF1β might indirectly regulate Trpm6 expression in the intestines and kidneys through FXR, contributing to disturbed Mg²⁺ homeostasis in HNF1β patients.

Although HNF1β is also expressed in the thick ascending limb of Henle’s loop (TAL) and this segment transports substantial amounts of Na⁺, K⁺, Ca²⁺, and Mg²⁺, the role of HNF1β in electrolyte transport in this segment...
remains elusive. In the TAL, HNF1β was demonstrated to regulate the expression of \textit{SLC12A1}, encoding the \textit{Na}⁺-\textit{K}⁺-\textit{Cl}⁻ co-transporter 2 (NKCC2) (Fig. 1) \cite{[36]}. As NKCC2 facilitates monovalent ion transport and provides
TAL AQP2 (FXR). In return, transcription factor FXR regulates expression of the subunit of the inward rectifier K⁺ channel (Kir5.1) and CASR sensing receptor (the expression of uromodulin (UMOD); ADTKD-HNF1β patients. 

Calcium levels in the blood. Nonetheless, hypocalcemia is not consistently observed in ADTKD-HNF1β patients. 

HNF1β is expressed in all tubule segments of the nephron [20]. Consequently, transcriptional targets of HNF1β have also been identified in the proximal tubule (PT). The expression of organic anion transporters (OAT1, OAT3, OAT4), the Na⁺-phosphate transporter 1 (NPT1), and the renal urate transporter (URAT1) is regulated by HNF1β (Fig. 1) [37–39, 66, 99]. Nevertheless, only a few individual cases were presenting with Fanconi syndrome, suggesting relatively mild PT dysfunction [28]. The absence of a PT phenotype in most patients can potentially be explained by the action of HNF1α, which may compensate for the loss of HNF1β in this segment. As HNF1α is within the kidney exclusively expressed in the PT, other nephron segments do not benefit from this compensatory action [100].

The role of HNF1β in ureteric bud branching and nephron patterning during kidney development

HNF1β has an essential role during kidney development [20, 32, 90]. The developmental defects may contribute to electrolyte disturbances observed in patients with ADTKD-HNF1β. In Gitelman syndrome, impaired DCT development has been postulated as one of the main causes of Mg²⁺ wasting [97]. Consequently, defects in kidney tubule patterning should be considered when studying the molecular pathogenesis of ADTKD-HNF1β. Various kidney-specific or inducible mice models have been generated over the past years to determine the role of HNF1β in kidney development (Table 1).

Mice with heterozygous Hnf1b null mutations have no phenotype, while complete deletion of Hnf1b in a mouse model is embryonically lethal due to its crucial role in embryonic visceral endoderm formation [21, 90]. Around E10.5, the development of the kidney starts with the outgrowth of the ureteric bud (UB) from the Wolffian duct
Table 1 Systematic comparison of all published Hnf1b mouse models

| Mouse model          | Genetic model | Electrolytephenotype | Developmental defects | Presence of cysts | Apico-basolateral polarity | Renal function | Survival | Other | Reference |
|----------------------|---------------|----------------------|-----------------------|-------------------|-----------------------------|----------------|----------|-------|-----------|
| Kidney               | KI            | Cdh16                | NR                    | NR                | NR                          | Normal to increased BUN levels | NR       | NR    | [106]    |
| Kidney               | KO Cre-loxP   | Cdh16                | NR                    | NR                | Abnormalities of mature nephrons | Similar number of cilia | Increased serum and urea creatinine | P10–P21 | Hydronephrosis (92%) Interstitial fibrosis (NR) | [32] [16] |
| Full body Inducible KO at P1 MxCre-LoxP | KO Cre-loxP | SIX2                  | NR                    | NR                | Delayed and defective UB branching Absence of MET and fewer MM condensations | NR         | Normal to increased BUN levels | NR       | NR    | [78]    |
| Full body Inducible KO at P10 MxCre-LoxP | KO Cre-loxP | Wnt4                 | NR                    | NR                | Absence of bulge in S-shaped body Rudimentary nephrons | +          | Correctly polarized RVs | NR       | NR    | [35]    |
| Full body with exception of ExEn | KO Cre-loxP | Wnt4                 | NR                    | NR                | Absence of bulge in S-shaped body Rudimentary nephrons | +          | Correctly polarized RVs | NR       | NR    | [35]    |

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Table 1 (continued)

| Mouse model | Genetic model | Electrolyte phenotype | Developmental defects | Presence of cysts | Apico-basolateral polarity | Renal function | Survival | Other | Reference |
|-------------|---------------|-----------------------|-----------------------|-------------------|---------------------------|----------------|----------|-------|-----------|
| CD          | KO Cre-loxP   | Pkd1                  | Reduced urine osmolality
Decreased Na⁺, K⁺, and urea
urine concentrations | NR                | +                        | +                | +                  | +                | NR          | Increased serum creatinine | Normal | Polyuria (NR) [3] |
| UB          | Mosaic KO Cre-loxP| HoxB7                 | Defective UB branching and CD differentiation | -                 | +                        | +                | -                  | Abnormal Fewer cilia | NR          | P2 to P15 | Hypoplasia (100%) [25] |
| Full body   | HET Splice-site mutation intron-2 | - | Reduced urine osmolality
Increased total Mg²⁺, Na⁺
and K⁺ urine excretion²
Increased urine Ca²⁺ | Delayed PT differentiation
Fewer glomeruli | +                        | +                | +                  | +                | Abnormal Fewer cilia | Normal plasma creatinine levels | P1 to P25 (10–15%)े | Hydronephrosis (33%)े | Duplicated kidney (17%े) | Polyuria (NR) [103] |

KI knock-in, BUN blood urea nitrogen, NR not reported, KO knock-out, ExEn extra-embryonic endoderm including visceral endoderm, UB ureteric bud, MET mesenchymal-epithelial transition, MM metanephric mesenchyme, RV renal vesicle, HET heterozygote, CD collecting duct, PT proximal tubules

²Nephron comprising a glomerulus connected to the collecting system by a short tubule displaying distal fates

³Age P7 and age > P35

⁴Age P35 and age > P35

⁵< 12 months of age

⁶In the C57BL/6 N background but not in 129sv background

References [3, 25, 103]
(WD) into the metanephric mesenchyme (MM) (Fig. 2). The UB undergoes branching morphogenesis to form the collecting duct system and ureter, after which MM cells surrounding the tips of the ureteric branches form cap mesenchyme. Triggered by signals from the UB tips, these cap mesenchymal cells will polarize into primitive epithelial spheres (pretubular aggregates) to form the renal vesicles. Renal vesicles differentiate into comma- and S-shaped bodies;
null
are rare in ADTKD-HNF1β, which is difficult to match with maldevelopment of the PT [28]. However, it should be noted that kidney development has been mostly studied in mice. In addition, PT defects could be compensated for by HNF1α transcriptional activity in postnatal life, as evidenced by partial restoration of several PT markers in adult kidneys of mice with a heterozygous splice site mutation in Hnf1b [103]. The impact of heterozygous mutations on kidney development in humans is largely unknown. Histological analysis of a limited number of cystic kidneys from human fetuses carrying HNF1β mutations showed defective or delayed nephrogenesis characterized by a decrease in nephrin structures labeled by either LTA, NKCC2, or UMOD [11, 34, 47]. How and to what extent, developmental abnormalities in mice and humans, in particular the rudimentary nephrons lacking mature PT, TAL, and DCT observed in mice models, influence ion transport in adults is unknown. In recent years, an impressive number of human kidney organoids models have been generated and successfully employed to improve our understanding of kidney diseases (reviewed in [104]). Hence, organoid models may provide a valuable tool to better understand the role of HNF1β in human kidney development and electrolyte transport using relevant genetic models instead of full KOs.

The role of HNF1β in apical-basolateral polarity, tight junction integrity, and primary cilia

Apical-basolateral polarity and tight junctions are key regulators of controlled water and ion movement in the kidney epithelium [24, 73]. Moreover, the primary cilium influences renal electrolyte transport in response to changes in tubular flow [52, 63, 72, 81]. In the following part of this review, we will discuss the proposed role of HNF1β in apical-basolateral polarity, tight junction function, and primary cilia development.

Apical-basolateral polarity

Apical-basolateral polarity allows the distribution of channels and transporters to distinct membrane domains and is critical for directional transport of ions and water from the pro-urine to the blood and vice versa [73]. Several polarity markers show aberrant localization or expression during kidney development in HNF1β mutant mice models [25, 103]. For instance, removal of Hnf1b from the UB in mice results in reduced expression of polarity markers Cdh16 and Pkd1 in UB epithelium [25]. Moreover, in mice with a heterozygous splice site mutation in Hnf1b, decreased levels of HNF1β appear to disturb basal membrane organization without affecting apical cell polarity markers [103]. Interestingly, NKCC2 expression in TAL cells, normally apically expressed, was normal in non-cystic tubules, but the expression was downregulated in cystic tissue [103]. Studies performed by our group using an immortalized mouse collecting duct cell line with disrupted HNF1β function demonstrated a decrease in cell height compared to cells expressing WT HNF1β (unpublished data). Apical-basal growth is a characteristic of polarizing epithelia; likewise, studies using different types of epithelial cells have shown that a loss of cell integrity is associated with a decrease in cell height [59, 71]. In addition, HNF1β+/− ureteric bud organoids derived from human iPS cells display loss of apical-basolateral polarity shown by reduced mRNA expression of apical markers, villin-2 (EZRIN) and protein kinase C zeta type (PRKCζ) [101]. Consistent with this putative role for HNF1β in establishing cell polarity, HNF1β-binding site motifs are enriched in ATAC-sequencing peaks and promoters of upregulated genes during in vitro 3D spheroid formation [105]. Together, this suggests that gene activation by HNF1β is important for cells to establish cell polarization.

Tight junction integrity

Tight junctions establish a border between the functionally different apical and basolateral membrane and act as a barrier for paracellular transport of water and ions [24, 89]. These structures contain a wide variety of proteins (occluding, claudins, junctional adhesion molecules) that define the permeability characteristics of epithelia [24, 58]. Structurally, Desgrange et al. showed that tight junctions appeared well-organized in the UB tips of developing Hnf1b mutant kidneys; however, lateral cell–cell junctions were irregular and the space between cells was larger [25]. Both disruptions in Ca^2+ and Mg^2+ homeostasis are frequently observed in ADTKD-HNF1β patients. Our unpublished data in immortalized cells showed a significant decrease in transepithelial resistance (TEER) values, a measure of paracellular pathway resistance involving tight junction integrity, in cells with disrupted HNF1β function compared to cells expressing WT Hnf1b.

Primary cilia development

HNF1β regulates an impressive number of genes that localize to the primary cilium including PKHD1, PKD1, PKD2, IFT88, KIF12, CYS1, and PDE4C (reviewed in [70]). Consequently, ciliary defects have been widely considered as the main cause of cyst formation in ADTKD-HNF1β patients [32, 70]. Nevertheless, it is unclear whether HNF1β is directly involved in primary cilium formation, despite the direct transcriptional activation of cilia genes. Two independent studies observed a decrease (25% and not quantified, respectively) of cilia in the cystic epithelium of developing mutant mice compared to WT mice [25, 103]. However, a different study observed normal cilia in cystic tubular cells.
The role of HNF1β in cilia function may also be relevant for electrolyte transport. The cilia acts as an antenna to sense tubular flow and converts changes in tubular pressure into signals that affect electrolyte transport along the nephron [52, 63, 72, 81]. Evidence for the involvement of cilia in flow sensing is based on the fact that flow-sensitive proteins polycystin 1 and transient receptor potential cation channel vanilloid-type 4 (TRPV4) localize to the primary cilium [43, 84, 87]. Furthermore, several examples demonstrate the putative importance of cilia in flow-mediated electrolyte transport. For instance, mice without ciliated TAL cells have diminished Na+ excretion in response to increased water intake causing differences in tubular pressure [72]. In addition, the removal of cilia in immortalized mouse DCT cells reduced transepithelial Ca2+ transport [52]. Additional quantitative studies and the use of high-resolution microscopy techniques to visualize key ciliary proteins should clarify whether HNF1β is involved in cilia function in the kidney.

The importance of cell polarity and tight junction integrity in ion homeostasis has been recognized for decades. Even though the analyzed studies demonstrate that HNF1β defects disturb apical-basolateral cell polarity and tight junction integrity, these mechanisms have never been considered in the pathogenesis of electrolyte disturbances observed in ADTKD-HNF1β patients [25, 103, 105]. Although many Hnf1b animal models have been developed, electrolyte disturbances and polarity defects are often not measured (Table 1). Systematic analysis of apical-basolateral polarity markers and intracellular signaling pathways may help further elucidate the role of cell polarity in electrolyte homeostasis.

**Additional pathways**

Our literature review has demonstrated that several mechanisms contribute to electrolyte disturbances in patients with HNF1β defects. Nevertheless, it cannot be excluded that additional factors influence ion transport in these patients.

Firstly, the presence of cysts in the kidneys of ADTKD-HNF1β patients can lead to electrolyte disturbances, as observed in patients with autosomal dominant polycystic kidney disease (ADPKD) [60, 62]. Interestingly, the deletion of a transcriptional target of HNF1β and frequently mutated gene in ADPKD patients, called Pkd1, caused aberrant Mg2+, Ca2+, and phosphate (P) handling in a pre cystic mice model [80]. Given the precystic stage of the mice, these changes could not be caused by dilated and cystic tubular structures but were instead attributed to the downregulation of key regulators in Mg2+ and Ca2+ reabsorption in the TAL (Cldn16, Kcnj1, Slc12a1), DCT (Trpm6, Slc12a3), and connecting tubule (Calb1, Slc8a1, Atp2b4). Several of these genes are also downregulated in (developing) kidney tissue of Hnf1b mutant mice [25, 50, 103]. The presence of cysts in glomerular and tubular nephron structures of ADPKD patients can dramatically impair electrolyte and water homeostasis. However, no association has been described to date between the presence of cysts and hypomagnesemia or other electrolyte phenotypes in ADTKD-HNF1β patients.

Secondly, in vitro and in vivo experiments have shown that HNF1β controls mitochondrial respiration in the PT [15, 61]. Inhibition or KO of HNF1β in a human PT cell line resulted in either downregulation of Pparc1a (important for mitochondrial biogenesis) and altered mitochondrial morphology or ATP reduction and increased glycolysis, respectively [15, 61]. The kidney requires large quantities of ATP to maintain electrochemical gradients across membranes which are particularly important for tran cellular ion transport [9]. Given the high energetic demand of the kidneys, the energy deficiency triggered by HNF1β defects might influence transport processes in the PT, and potentially TAL and DCT-mediated transport of Mg2+, Ca2+, and K+. Indeed, mutations in the mitochondrial DNA were recently demonstrated to cause a Gitelman-like phenotype of hypomagnesemia and hypokalemia [82].

Finally, over the past years, HNF1β has been implicated in a broad spectrum of pathways ranging from WNT signaling to planar cell polarity and cholesterol synthesis [1, 17, 31]. The role of these pathways in electrolyte transport has never been examined.

**Conclusions and perspectives**

Hypomagnesemia, hyperuricemia, and hypocaliuria are common in patients with ADTKD-HNF1β. In subgroups of patients, these electrolyte disturbances are associated with hyperparathyroidism, hypokalemia, and metabolic alkalosis. These clinical findings suggest that the electrolyte disturbances in patients with HNF1β defects have a distal tubular origin. Indeed, our literature review demonstrated that HNF1β regulates the expression of genes involved in distal tubule electrolyte transport, including FXYD2, KCNJ16, CASR, and FXR. In this review, we propose additional mechanisms that may further contribute to electrolyte disorders. HNF1β defects have been demonstrated to impair kidney development, apical-basolateral polarity, tight junction integrity, and cilia development.

The function of HNF1β in kidney physiology has mainly been studied in a wide range of mouse models. Our systematic comparison of all published mouse models identified large differences in phenotypes depending on the genetic
defect and strain (Table 1). Complete HNF1β KO may result in different molecular consequences than heterozygous deletions and missense mutations. Consequently, the pathophysiological mechanism of ADTKD-HNF1β may not be captured by most available mouse studies. Moreover, phenotyping of the electrolyte disturbances in HNF1β patients and mouse models is limited, resulting in a knowledge gap in the literature. A more systematic approach is required to associate specific polarity, cilia, or tight junction defects with electrolyte disturbances.

A promising development is the generation of organoid models from patient-derived iPSCs. Recently, kidney organoids were successfully generated from urinary iPSCs of HNF1β patients [53]. Although the current generation kidney organoids are still immature compared with fetal and adult human kidney, these models provide the first patient-derived model to study HNF1β defects in kidney development and function [85].

In conclusion, the causes of electrolyte disturbances in ADTKD-HNF1β may partially be beyond direct transcriptional regulation of specific channels and transporters. Further studies should determine which additional pathways contribute to the molecular mechanisms of electrolyte disturbances observed in ADTKD-HNF1β patients. More systematic phenotyping and the development of patient-specific organoid models are essential next steps in HNF1β research.

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Declarations

Conflict of interest  The authors declare no competing interests.

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References

1. Aboudehen K, Kim MS, Mitsche M, Garland K, Anderson N, Noureddine L, Pontoglio M, Patel V, Xie Y, DeBoer-Boyd R, Igarashi P (2016) Transcription factor hepatocyte nuclear factor-1 regulates renal cholesterol metabolism. J Am Soc Nephrol 27:2408–2421. https://doi.org/10.1681/ASN.2015060607
2. Aboudehen K, Noureddine L, Cobo-stark P, Avdulov S, Igarashi P (2017) Hepatocyte nuclear factor–1β regulates urinary concentration and response to hypertonicity. J Am Soc Nephrol 28:2887–2900
3. Aboudehen K, Noureddine L, Cobo-stark P, Avdulov S, Farahani S, Gearhart MD, Bichet DG, Pontoglio M, Patel V, Igarashi P (2017) Hepatocyte nuclear factor–1 β regulates urinary concentration and response to hypertonicity. J Am Soc Nephrol 28:2887–2900. https://doi.org/10.1681/ASN.2016101095
4. Adalat S, Woolf AS, Johnstone KA, Wissing A, Harries LW, Long DA, Hennekam RC, Lederman SE, Rees L, Van HW, Marks SD, Trompetter RS, Tullus K, Winyard PJ, Canjsick J, Mushtaq I, Dhillon HK, Bingham C, Edghill EL, Shroff R, Stanescu H, Ryffel GU (2009) HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. J Am Soc Nephrol 20:1123–1131
5. Adalat S, Woolf AS, Johnstone KA, Wissing A (2009) HNF1B mutations associate with hypomagnesemia and renal magnesium. J Am Soc Nephrol 20:1123–1131
6. Adalat S, Hayes WN, Bryant WA, Booth J, Woolf AS, Kleta R, Subtil S, Clissold R, Colclough K, Ellard S, Bockenhauer D (2019) HNF1B mutations are associated with a Gitelman-like tubulopathy that develops during childhood. Kidney International Reports 4:1304–1311. https://doi.org/10.1016/j.ekir.2019.05.019
7. Ashton EJ, Legrand A, Benoit V, Roncelin I, Venisse A, Zennaro MC, Jeunemaitre X, Iancu D, van’t Hoff WG, Walsh SB, Godefroid N, Rotthier A, del Favero J, Devuyst O, Schaefier F, Jenkins LA, Kleta R, Dahan K, Vargas-Pousou R, Bockenhauer D (2018) Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies. Kidney Int 93:961–967
8. Bech AP, Wetzels JF, Bongers EMHF, Nijenhuis T (2016) Thiouacid responsiveness testing in patients with renal magnesium wasting and correlation with genetic analysis: a diagnostic test study. Am J Kidney Dis 68:168–170
9. Bhargava P, Schneilmann RG (2017) Mitochondrial energetics in the kidney. Nat Rev Nephrol 13:629–646
10. Bingham C, Hattersley AT (2004) Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1β. Nephrol Dial Transplant 19:2703–2708
11. Bingham C, Ellard S, Allen L, Bulman M, Shepherd M, Frayling T, Berry PJ, Clark PM, Lindner T, Bell GI, Ryffel GU, Nicholls AJ, Hattersley AT (2000) Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1β. Kidney Int 57:898–907
12. Bockenhauer D, Jaureguiberry G (2016) HNF1B-associated clinical phenotypes: the kidney and beyond. Pediatr Nephrol 31:707–714. https://doi.org/10.1007/s00467-015-3142-2
13. Bockenhauer D, Feather S, Stanescu H, Bandulik S, Zdebik AA, Reicheold M, Tobin J, Lieberer E, Sterner C, Landoure G, Arora R, Srimannana T, Thompson D, Cross JH, van’t Hoff W, al Masri O, Tullus K, Yeung S, Anikster Y, Klootwijk E, Hubank M, Dillon MJ, Heitzmann D, Arcos-Burgos M, Knepper MA, Dobbie A, Gahl WA, Warth R, Sheridan E, Kleta R (2009) Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. N Engl J Med 360:1960–1970
14. Brunskill EW, Aronow BJ, Georgas K, Rumballe B, Valerius MT, Aronow J, Kaimal V, Jegga AG, Grimson S, McMahon AP, Patterson LT, Little MH, Potter SS (2008) Atlas of gene expression in the developing kidney at microarray resolution. Dev Cell 15:781–791. https://doi.org/10.1016/j.devcel.2008.09.007

15. Casemyou A, Fournel A, Bagattin A, Schanstra J, Bellen J, Decramer S, Marsal D, Gillet M, Chassaing N, Huart A, Pontoglio M, Knauf C, Bascands J-L, Chauveau D, Faguer S (2017) Hepatocyte nuclear factor-1 β controls mitochondrial respiration in renal tubular cells. J Am Soc Nephrol 28:3205–3217

16. Chan SC, Zhang Y, Shao A, Avdulov S, Herrera J, Aboudehen K, Pontoglio M, Igarashi P (2018) Mechanism of fibrosis in HNF1B-related autosomal dominant tubulointerstitial kidney disease. J Am Soc Nephrol 29:2493–2509. https://doi.org/10.1681/ASN.2018040437

17. Chan SC, Zhang Y, Pontoglio M, Igarashi P (2019) Hepatocyte nuclear factor-1 β regulates Wnt signaling through genome-wide competition with β-catenin/lymphoid enhancer binding factor. Proc Natl Acad Sci USA 116:24133–24142. https://doi.org/10.1073/pnas.1909452116

18. Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham RJ (2018) Autosomal dominant tubulointerstitial kidney disease. Kidney Int 92:1145–1156

19. Clissold RL, Shaw-Smith C, Turnpenny P, Bunce B, Bockenhauer D, de Baaij JHF, Dorresteijn EM, Hennekam EAM, Kamsteeg EJ, Coffinier C, Gresh L, Fiette L, Tronche F, Schütz G, Babinet C (2019) Expression of HNF1B controls epithelial organization and cell polarity during mouse organogenesis. Mech Dev 129:1829–1838

20. Coffinier C, Barra J, Babinet C, Yaniv M (1999) Expression of the vHNF1/HNF1β homeoprotein gene during mouse organogenesis. Mech Dev 89:211–213

21. Coffinier C, Barra J, Babinet C, Yaniv M (1999) Expression of the vHNF1/HNF1β homeoprotein gene during mouse organogenesis. Mech Dev 89:211–213

22. Coffinier C, Gresh L, Fiette L, Tronche F, Schütz G, Babinet C, Pontoglio M, Yaniv M, Barra J (2002) Bile system morphogenesis defects and liver dysfunction upon targeted deletion of HNF1β. Dev 129:1829–1838

23. de Baaij JHF, Dorresteijn EM, Hennekam EAM, Kamsteeg EJ, Meijer R, Dahan K, Muller M, van den Dorpel MA, Bindels RJM, Hoenderop JGJ, Devuyst O, Knoers NVAM (2015) Recurrent FXYD2 p.Gly41Arg mutation in patients with isolated dominant hypomagnesaemia. Nephrol Dial Transplant 30:952–957.

24. Denker BM, Sabath E (2011) The biology of epithelial cell tight junctions in the kidney. J Am Soc Nephrol 22:622–625

25. Desgrange A, Heliot C, Skovorodkin I, Akram SU, Heikkilä J, Desgrange A, Heliot C, Buisson I, Prunskaite-Hyyryläinen R, JGJ (2016) Chromosome 17q12 microdeletions but not intragenic mutations link developmental kidney disease and psychiatric disorder. Kidney Int 90:203–211. https://doi.org/10.1016/j.kint.2016.03.027

26. Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J (2017) Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocellular nuclear factor 1B (HNF1B) molecular defects. Diabetes Care 40:1436–1443

27. Eckardt KU, Alper SL, Antignac C, Bleyer AJ, Chauveau D, Dahan K, Dela S, Hosking A, Knoch O, Srapolds L, Wiesener M, Wolf MT, Devuyst O (2015) Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management - A KDIGO consensus report. Kidney Int 88:676–683

28. Faguer S, Decramer S, Chassaing N, Bellanné-Chantelot C, Calvas P, Beaufils S, Bessenay L, Lengelé JP, Dahan K, Ronco P, Devuyst O, Chauveau D (2011) Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int 80:768–776. https://doi.org/10.1038/ki.2011.225

29. Faguer S, Chassaing N, Bandin F, Prouzeau C, Garnier A, Casemyou A, Huart A, Schanstra JP, Calvas P (2014) The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int 86:1007–1015

30. Ferré S, Bongers EMHF, Sonneveld R, Cornelissen EAM, van der Vlag J, van Boekel GAJ, Wetzels JFM, Hoenderop JGJ, Bindels RJM, Nijenhuis T (2013) Early development of hyperparathyroidism due to loss of PTH transcriptional repression in patients with HNF1/β mutations? J Clin Endocrinol Metab 98:4089–4096

31. Fischer E, Legue E, Doyen A, Nato F, Nicolas JF, Torres V, Yaniv M, Pontoglio M (2006) Defective planar cell polarity in polycystic kidney disease. Nat Genet 38:21–23. https://doi.org/10.1038/ng1701

32. Gresh L, Fischer E, Tanguy M, Shao X, Hiesberger T, Fiette L, Igarashi P, Pontoglio M (2004) A transcriptional network in polycystic kidney disease. EMBO J 23:1657–1668

33. Haumaitre C, Barbacci E, Jenny M, Ott MO, Gradwohl G, Cereghini S (2005) Lack of TCF/βHNF1 in mice leads to pancreas agenesis. PNAS 102:1490–1495

34. Haumaitre C, Fabre M, Cormier S, Baumann C, Deleziole AD, Cereghini S (2006) Severe pancreas hypoplasia and multicystic renal dysplasia in two human fetuses carrying novel HNF1β/MODY5 mutations. Hum Mol Genet 15:2363–2375

35. Heliot C, Desgrange A, Buisson I, Prunskaite-Hyyryläinen R, Shang J, Vainio S, Umbauer M, Cereghini S (2013) HNF1β controls proximal-intermediate nephron segment identity in vertebrates by regulating Notch signalling components and Irx1/2.

36. Igarashi P, Whyte DA, Li K, Nagami GT (1996) Cloning and kidney cell-specific activity of the promoter of the murine renal Na-K-Cl cotransporter gene. J Biol Chem 271:9666–9674. https://doi.org/10.1074/jbc.271.16.9666

37. Jin L, Kikuchi R, Saji T, Kusuhara H, Sugiyama Y (2012) Regulation of tissue-specific expression of renal organic anion transporters by hepatocyte nuclear factor 1α/β and DNA methylation. J Pharmacol Exp Ther 29:648–655

38. Kikuchi R, Kusuhara H, Hattori N, Shiota K, Gonzalez FJ, Sugiyama Y (2006) Regulation of the expression of human organic anion transporter 3 by hepatocyte nuclear factor 1α/β and DNA methylation. Mol Pharmacol 70:887–896. https://doi.org/10.1124/mol.106.025494

39. Kikuchi R, Kusuhara H, Hattori N, Kim I, Gonzalez FJ, Shiota K, Gonzalez FJ, Sugiyama Y (2007) Regulation of tissue-specific expression of the human and mouse urate transporter 1 gene by hepatocyte nuclear factor 1α and DNA methylation. Mol Pharmacol 72:1619–1625

40. Kim EY, Lee JM (2022) Transcriptional control of Trpm6 by the nuclear receptor FXR. Int J Mol Sci 23:1980

41. Kompatscher A, de Baaij JHF, Aboudehen K, Hoefnagels APWM, Igarashi P, Bindels RJM, Veenstra GJC, Hoenderop JGJ (2017) Loss of transcriptional activation of the potassium channel Kir5.1 by HNF1β drives autosomal dominant tubulointerstitial kidney disease. Kidney Int 92:1145–1156

42. Kompatscher A, de Baaij JHF, Aboudehen K, Farahani S, van Son LHH, Milatz S, Himmerkus N, Veenstra GC, Hoenderop JGJ (2018) Transcription factor HNF1B regulates expression of the calcium-sensing receptor in the thick ascending limb of the kidney. Am J Renal Physiol 315:F27–F35

43. Kunnen SJ, Malas TB, Formica C, Leonhard WN, ’t Hoen PAC, Peters DIM (2018) Comparative transcriptomics of shear stress treated Pkd1 +/−/ cells and pre-cystic kidneys reveals pathways involved in early polycystic kidney disease. Biomed
Pharmacother 108:1123–1134. https://doi.org/10.1016/j.biopharm.2018.07.178
44. Lindström NO, Mcmahon JA, Guo J, Tran T, Guo Q, Rutledge E, Parvez RK, Saribekyan G, Schuler RE, Liao C, Kim AD, Abdelhalim A, Ruffins SW, Thornton ME, Basking L, Grubbs B, Kesselman C, Mcmahon AP (2018) Conserved and divergent features of human and mouse kidney organogenesis significance statement. J Am Soc Nephrol 29:785–805
45. Lokmane L, Haumaire C, Garcia-Villalba P, Anselme I, Schnei-
der-Mauonnay S, Cereghini S (2008) Crucial role of vHNF1 in vertebrate hepatic specification. Dev 135:2777–2786
46. Lokmane L, Heliot C, Garcia-villalba P, Fabre M, Cereghini S (2010) vHNF1 functions in distinct regulatory circuits to control ureteric bud branching and early nephrogenesis. Dev 137:347–357
47. Madariaga L, Moriníere V, Jeanpierre C, Bouvier R, Loget PB, Martinovic J, Dechelotte P, Lopporier N, Thavun-Robinet C, Jensen UB, Gaillard D, Mathieu M, Turlin B, Attie-Bitach T, Salomon R, Gührer MC, Antignac C, Heidet L (2013) Severe prenatal renal anomalies associated with mutations in HNF1B or PAX2 genes. Clin J Am Soc Nephrol 8:1179–1187
48. Madariaga L, García-Castaño A, Ariceta G, Martínez-Salazar R, Aguayo A, Castaño L (2019) Variable phenotype in HNF1B mutations: extrarenal manifestations distinguish affected individ-
uals from the population with congenital anomalies of the kidney and urinary tract. Clin Kidney J 12:373–379. https://doi.org/10.1016/j.clkj.2019.01.002
49. Martínez V, Trasancos C, Ramos F, Álcazar C, Cabezuelo JB, Garcia M (2016) Poliquistosis renal autosómica recesiva diagnosti-
cada en mujer de 39 años con fallo renal y calambres. Nef-
rología 36:318–320. https://doi.org/10.1016/j.nefro.2016.02.002
50. Massa F, Garbay S, Bourvier R, Sugitani Y, Noda T, Gubler M-C, Heidet L, Pontoglio M, Fischer E (2013) Hepatocyte nuclear fac-
tor 1 controls nephron tubular development. Dev 140:886–896
51. Mej I, Koeanderink JB, de Jong JC, de Pont JIHHM, Monmens LAH, van den Heuvel LPWJ, Knoers NVAM (2003) Dominant isolated renal magnesium loss is caused by misrouting of the LAH, van den Heuvel LPWJ, Knoers NVAM (2003) Dominant
52. Nagano C, Morisada N, Nozu K, Kamei K, Tanaka R, Kanda S, Bockenhauer D, Konrad M (2018) Germline de novo mutations in ATPT1A cause renal hypomagnesemia, refrac-
tory seizures, and intellectual disability. Am J Hum Genet 2018. 07. 178
53. Okorn C, Goertz A, Vester U, Beck BB, Bergmann C, Habbig S, König J, Konrad M, Müller D, Oh J, Ortiz-brüchle N, Patzer L, Schild R, Seeman T, Staude H, Thumbart J, Tönshoff B, Walden U, Weber L, Weber S (2019) HNF1B nephropathy has a slow-
progressive phenotype in childhood—with the exception of very early onset cases: results of the German Multicenter HNF1B Childhood Registry. Pediart Nephrol 34:1065–1075
54. Otsu T, Furuse M (2020) Tight junction structure and function revisited. Trends Cell Biol 30:805–817
55. Okorn C, Goertz A, Vester U, Beck BB, Bergmann C, Habbig S, König J, Konrad M, Müller D, Oh J, Ortiz-brüchle N, Patzer L, Schild R, Seeman T, Staude H, Thumbart J, Tönshoff B, Walden U, Weber L, Weber S (2019) HNF1B nephropathy has a slow-
progressive phenotype in childhood—with the exception of very early onset cases: results of the German Multicenter HNF1B Childhood Registry. Pediart Nephrol 34:1065–1075
56. Nie M, Bal MS, Liu J, Yang Z, Rivera C, Wu XR, Hoender
cell tubular cells. FASEB J 35:1–16
57. Okorn C, Goertz A, Vester U, Beck BB, Bergmann C, Habbig S, König J, Konrad M, Müller D, Oh J, Ortiz-brüchle N, Patzer L, Schild R, Seeman T, Staude H, Thumbart J, Tönshoff B, Walden U, Weber L, Weber S (2019) HNF1B nephropathy has a slow-
progressive phenotype in childhood—with the exception of very early onset cases: results of the German Multicenter HNF1B Childhood Registry. Pediart Nephrol 34:1065–1075
acid-base homeostasis, and sensorineural deafness. J Am Soc Nephrol 32: 1498–1512.
69. Seeman T, Weigel F, Blahova K, Fencí F, PruhoVA S, Hermes K, Klaus R, Lange-Sperandio B, Grote V, John-Kroegel U (2021) Blood pressure in children with renal cysts and diabetes syndrome. Eur J Pediatr 180: 3599–3603.
70. Shao A, Chan SC, Igarashi P (2020) Role of transcription factor hepatocyte nuclear factor 1-β in polycystic kidney disease. Cell Signal 71: 1-24. https://doi.org/10.1016/j.cellsig.2020.105686
71. Shen L, Weber CR, Raleigh DR, Yu D, Turner JR (2011) Tight junction pore and leak pathways: a dynamic duo. Annu Rev Physiol 72: 283–309.
72. Song J, Wang L, Fan F, Wei J, Zhang J, Lu Y, Fu Y, Wang S. Juncos LA, Liu R (2017) Role of the primary cilia on the macula densa and thick ascending limbs in regulation of sodium excretion and hemodynamics. Hypertens 70: 324–333.
73. Stoops EH, Caplan MJ (2014) Trafficking to the apical and basolateral membranes in polarized epithelial cells. J Am Soc Nephrol 25: 1375–1386.
74. Sugimoto R, Watanabe H, Ikekagi K, Enoki Y, Imafuku T, Sakaguchi Y, Murata M, Nishida K, Miyamura S, Ishima Y, Tanaka M, Matsushita K, Komaba H, Fukagawa M, Otagiri M, Maruyama T (2017) Down-regulation of ABCG2, a urate exporter, by parathyroid hormone enhances urate accumulation in secondary hyperparathyroidism. Kidney Int 91: 658–670.
75. Tokonami N, Takata T, Beyer J, Ehrbar I, Yoshifuji A, Chris-tof JF, Patel C, Shenoy M, Steenbergen EJ, Anderson G, Bongers Vallet M, Decramer S, Pelletier S, Klaus G, Kömhoff M, Beetz A, Chan MMY, van Beek A, van Eerde AM, Coulibaly J-M, Tobe SW, Farhi A, Nelson-Williams C, Lifton LP (2016) The excretion of uromodulin is modulated by the calcium-sensing receptor. Kidney Int 94: 701–715.
76. Tokonami N, Olinger E, Debaix H, Houillier P, Devuyst O (2018) The excretion of uromodulin is modulated by the calcium-sensing receptor. Kidney Int 94: 882–886.
77. van der Made CI, Hoor EJ, de La Faille R, Karaaslan H, Knoers NVAM, Hoenderop JGJ, Vargas Poussou R, de Baaij JHF (2015) Hypomagnesemia as first clinical manifestation of ADTKD-HNF1B: a case series and literature review. Am J Nephrol 42: 85–90. https://doi.org/10.1159/000439286
78. Verdegueur F, Le Corre S, Fischer E, Callens C, Garbay S, Doyen A, Igarashi P, Terzi F, Pontoglio M (2010) A mitotic transcriptional switch in polycystic kidney disease. Nat Med 16: 106–111.
79. Verhave JC, Bech AP, Wetzels JFM, Nijenhuis T (2016) Hepatocyte nuclear factor 1-β associated kidney disease: more than renal cysts and diabetes. J Am Soc Nephrol 27: 345–353.
80. Verschuren EHJ, Mohammed SG, Leonhard WN, Overmars-Bos C, Verraar K, Hoenderop JGJ, Bindels RJM, Peters DJM, Arjona FJ (2018) Polycystin-1 dysfunction impairs electrolyte and water handling in a renal precystic mouse model for ADPKD. Am J Physiol Renal Physiol 315: F537–F546.
81. Verschuren EHJ, Castenmiller C, Peters DJM, Arjona FJ, Bindels RJM, Hoenderop JGJ (2020) Sensing of tubular fluid and renal electrolyte transport. Nat Rev Nephrol 16: 337–351. https://doi.org/10.1038/s41581-020-0259-8.
82. Viering D, Schlingmann KP, Hureaux M, Nijenhuis T, Mallett A, Chan MMY, van Beek A, van Eerde AM, Coulibaly J-M, Vallet M, Decramer S, Pelletier S, Klaus G, Körnholff M, Beetz R, Patel C, Shenoy M, Steenbergen EJ, Anderson G, Borgers EMHF, Bergmann C, Panneman D, Rodenburg RJ, Kleta R, Houillier P, Konrad M, Vargas-Poussou R, Knoers NVAM, Bockenhauer D, de Baaij JHF (2022) Gitelman-like syndrome caused by pathogenic variants in mtDNA. J Am Soc Nephrol 33: 305–325.
83. Wolf MTF, Wu XR, Huang CL (2013) Uromodulin upregulates TRPV5 by impairing caveolin-mediated endocytosis. Kidney Int 84: 130–137.
84. Wu L, Gao X, Brown RC, Heller S, O’Neil RG (2007) Dual role of the TRPV4 channel as a sensor of flow and osmolality in renal epithelial cells. Am J Physiol Renal Physiol 293: 1699–1713.
85. Wu H, Uchimura K, Donnelly EL, Kiriti Y, Morris SA, Humphreys BD (2018) Comparative analysis and refinement of human PSC-derived kidney organoid differentiation with single-cell transcriptomics. Cell Stem Cell 23: 869–881.e8. https://doi.org/10.1016/j.stem.2018.10.010
86. Yi-zhi C, Qing GAO, Xue-zhi Z, Ying-zhang C, Bennett CL, Xi-shan X, Chang-lin MEI, Yong-quan SHI, Xiang-mei C (2010) Systematic review of TCF2 anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J 123: 3326–3333.
87. Yoder BK, Hou X, Guay-Woodford LM (2002) The polycys-tic kidney disease proteins, polycystin-1, polycystin-2, polars, and cystin, are co-localized in renal cilia. J Am Soc Nephrol 13: 2508–2516.
88. Zhang X, Huang S, Gao M, Liu J, Jia X, Han Q, Zheng S, Miao Y, Li S, Weng H, Xia Y, Xu D, Su W, Gustafsson JA, Guan Y (2014) Farnesoid X receptor (FXR) gene deficiency impairs urine concentration in mice. Proc Natl Acad Sci USA 111: 2277–2282.
89. Zihani C, Mills C, Matter K, Balda MS (2016) Tight junctions: from simple barriers to multifunctional molecular gates. Nat Rev Mol Cell Biol 17: 564–580. https://doi.org/10.1038/nrm.2016.80.
90. Barbacci E, Reber M, Ott M, Breillat C, Huetz F, Cereghini S (1999) Variant hepatocyte nuclear factor 1 is required for visceral endoderm specification. 8405: 4795–4805.
91. Owen K (2014) HNF1B-related autosomal dominant tubulointer-stitial kidney disease. In: Orphanet. Accessed 02-20-2022 https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=93111.
92. Kolbuc M, Bienias B, Habbig S, Kolek M, Szczepanska M, Kiliś-Prusiańska K, Wasilewska A, Adamczyk P, Motyka R, Tkacz-yk M, Sikora P, Beck BB, Zanie M (2021) Hyperuricemia is relatively common in children with HNF1B mutation, but its usefulness as a clinically useful marker for predicting the mutation is limited. Nephrol Dial Transplant 36. https://doi.org/10.1093/ndt/gfab080.0015.
93. Knoers NVAM, Levitschenko EN (2008) Gitelman syndrome. Orphanet J Rare Dis 3.
94. Simon DB, Nelson-Williams C, Johnson Bia M, Ellison D, Karet FE, Morey Molina A, Vuara I, Iwata F, Cusnher HM, Koolen M, Gcaniza FJ, Gitelman HJ, Lifton LP (1996) Gitelman’s variant of Bartter’s syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-CI cotransporter.
95. Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB (2001) Gitel-man’s syndrome revisited: An evaluation of symptoms and health-related quality of life. Kidney Int 59: 710–717. https://doi.org/10.1046/j.1523-1755.2001.0059021710.x.
96. Ferré S, Igarashi P (2018) New insights into the role of HNF-1β in kidney (patho)physiology. Pediatric Nephrol 1–11. https://doi.org/10.1007/s00467-018-3990-7.
97. Franken GAC, Adella A, Bindels RJM, de Baaij JHF (2021) Mechanisms coupling sodium and magnesium reabsorption in the distal convoluted tubule of the kidney. Acta Physiologica 231.
98. Scholl UI, Choi M, Liu T, Ramaekers VT, Hä Usler C MG, Grimmer J, Tobe SW, Farhi A, Nelson-Williams C, Lifton RP (2018) Seizures, sensorineural deafness, ataxia, mental retardation, and hyperuricemia (SeSAME syndrome) caused by mutations in KCNJ10.
99. Cheret C, Doyen A, Yaniv M, Pontoglio M (2002) Hepatocyte nuclear factor 1 controls renal expression of the Npt1-Npt4 anionic transporter locus. 2836: 929–941. https://doi.org/10.1016/S0022-2836(02)00816-1.
100. Pontoglio M, Barra J (1996) Hepatocyte nuclear factor 1 inactivation results in hepatic dysfunction, phenylketonuria, and renal Fanconi syndrome

101. Mae SI, Ryosaka M, Sakamoto S, Matsuse K, Nozaki A, Igami M, Kabai R, Watanabe A, Osafune K (2020) Expansion of human iPSC-derived ureteric bud organoids with repeated branching potential. Cell Rep 32. https://doi.org/10.1016/j.celrep.2020.107963

102. Miao Z, Balzer MS, Ma Z, Liu H, Wu J, Shrestha R, Aranyi T, Kwan A, Kondo A, Pontoglio M, Kim J, Li M, Kaestner KH, Susztak K (2021) Single cell regulatory landscape of the mouse kidney highlights cellular differentiation programs and disease targets. Nat Comm 12:2277. https://doi.org/10.1038/s41467-021-22266-1

103. Niborski LL, Paces-Fessy M, Ricci P, Bourgeois A, Magalhaes P, Kuzma-Kuzniarska M, Lesaulnier C, Reczko M, Declercq E, Zurbig P, Doucet A, Umbhauser M, Cereghini S (2021) Hnf1b haploinsufficiency differentially affects developmental target genes in a new renal cysts and diabetes mouse model. Dis Model Mech 14. https://doi.org/10.1242/dmm.047498

104. Romero-Guevara R, Ioannides A, Xinaris C (2020) Kidney Organoids as Disease Models: Strengths, Weaknesses and Perspectives. Front Phys 11:563981. https://doi.org/10.3389/fphys.2020.563981

105. Wang T, Kwon SH, Peng X, Urudy S, Lu Z, Schmitz RJ, Dalton S, Mostov KE, Zhao S (2020) A qualitative change in the transcriptome occurs after the first cell cycle and coincides with lumen establishment during MDCKII cystogenesis. iScience 23:101629. https://doi.org/10.1016/j.isci.2020.101629

106. Hiesberger T, Bai Y, Shao X, Mcnally BT, Sinclair AM, Tian X, Somlo S, Igarashi P (2004) Mutation of hepatocyte nuclear factor-1β inhibits Pkhd1 gene expression and produces renal cysts in mice. J Clin Invest 113

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