# Genetic Tubulointerstitial Disease and Nephronophthisis

*Alice Gage, Buddhika Illeperuma, and Mark Harber*

## Contents



© Springer Nature Switzerland AG 2022
M. Harber (ed.), *Primer on Nephrology*, https://doi.org/10.1007/978-3-030-76419-7_34

**Learning Objectives**

1. To cover and appreciate the nature, epidemiology and diagnosis of autosomal dominant tubulointerstitial renal diseases
2. To cover the nature, diagnosis and characteristics of autosomal recessive nephronophthisis conditions

**Definition**

ADTKD is a group of conditions characterised by chronic tubulointerstitial disease and progressive chronic kidney disease (CKD) in the context of a bland urine, with an autosomal dominant pattern of inheritance.

Nephronophthisis (NPHP) is a group of ciliopathies commonly causing end-stage renal disease in childhood and adolescence, characterised by chronic tubulointerstitial disease and progressive CKD in the context of a bland urine with an autosomal recessive pattern of inheritance.

34

## 34.1 Introduction

In 2015, KDIGO produced a consensus report which proposed the current classification of ADTKDs to replace previous nomenclature which included 'medullary cystic kidney disease' as well as providing guidance on diagnosis and management which has enhanced awareness and understanding of these conditions [1]. The main genes associated with ADTKD are *UMOD*, *MUC1*, *REN* and *HNF1B*, although new mutations and genes allied to this group continue to be discovered. They share an inconspicuous renal presentation, with the not infrequent occurrence of cysts which can be cortical or medullary and do not usually result in renal enlargement. However, there are some clinical clues to indicate the pathological process and differentiate between the individual diseases (Fig. 34.1). The current state of knowledge with ADTKDs is very nicely reviewed by Devuyst et al. [2].

These conditions range from rare to very rare, although it is likely that they are underdiagnosed given the paucity of constitutional symptoms or urinary findings that normally trigger investigation. A recent analysis of patients with end-stage renal failure in Ireland found a prevalence of 0.54% with a mutation consistent with ADTKD; this group comprised 42.6% *MUC1*, 32.5% UMOD and 13% *NHF1-β* mutations [3]. An increased awareness of these conditions is likely to result in a greater prevalence and earlier diagnosis as well as the discovery of new mutations.

Inherited renal ciliopathies include ADPKD, X-linked disorders such as oral-facial-digital syndrome and a heterogeneous but important group of autosomal recessive conditions such as ARPKD (discussed elsewhere) and nephronophthisis. Nephronophthisis also results in progressive Chronic kidney disease (CKD) characterised by interstitial fibrosis and tubular atrophy (IFTA) and sometimes microcytes as a result of genetic disorders of the cilium. Urine analysis in these patients is also bland and often shows concentration defects. Nephronophthisis is the commonest monogenic cause of ESRD in the first three decades of life. Moreover, in 10–20% of cases, nephronophthisis is associated with significant syndromic findings that result in a much earlier diagnosis as well as long-term disability.

Between nephronophthisis and ADTKD, there is a moderate portion of chronic kidney disease that needs diagnosis and management.

## 34.2 ADTKD

Autosomal dominant tubulointerstitial kidney diseases (ADTKD).

## 34.3 ADTKD-UMOD

Uromodulin (also known as Tamm-Horsfall glycoprotein) is a genuinely fascinating molecule produced solely in the kidney and with pleiotropic roles [4]. These include preventative roles in stone formation by reducing aggregation of calcium in super-saturated filtrate and urinary tract infection by binding to uropathogenic *E. coli* inhibiting bacterial adhesion to uroepithelial cells. It is also involved in salt and water regulation via the NKCC2 co-transporter and potassium ROMK channel as well as being implicated in innate immunity and immune regulation within the kidney. In this context, variants of uromodulin have been associated with a propensity to stone formation, CKD and hypertension in the general population.

ADTKD-UMOD is probably the commonest form of ADTKD, with one UK study finding a prevalence of 2% in ESRD patients [5]. It results from mutations in the uromodulin gene that are mostly missense mutations causing disruption of conserved cysteine residues and resulting in misfolding of the mature protein.

### 34.3.1 Aetiology and Pathogenesis

Misfolded uromodulin is abnormally trafficked with reduced expression on the apical surface of the epithelial cell and progressive accumulation in the endoplasmic reticulum particularly in the thick ascending limb (TAL). This results in ER stress, apoptosis, progressive interstitial fibrosis, tubular atrophy, microcyst formation and a secondary inflammatory infiltrate.

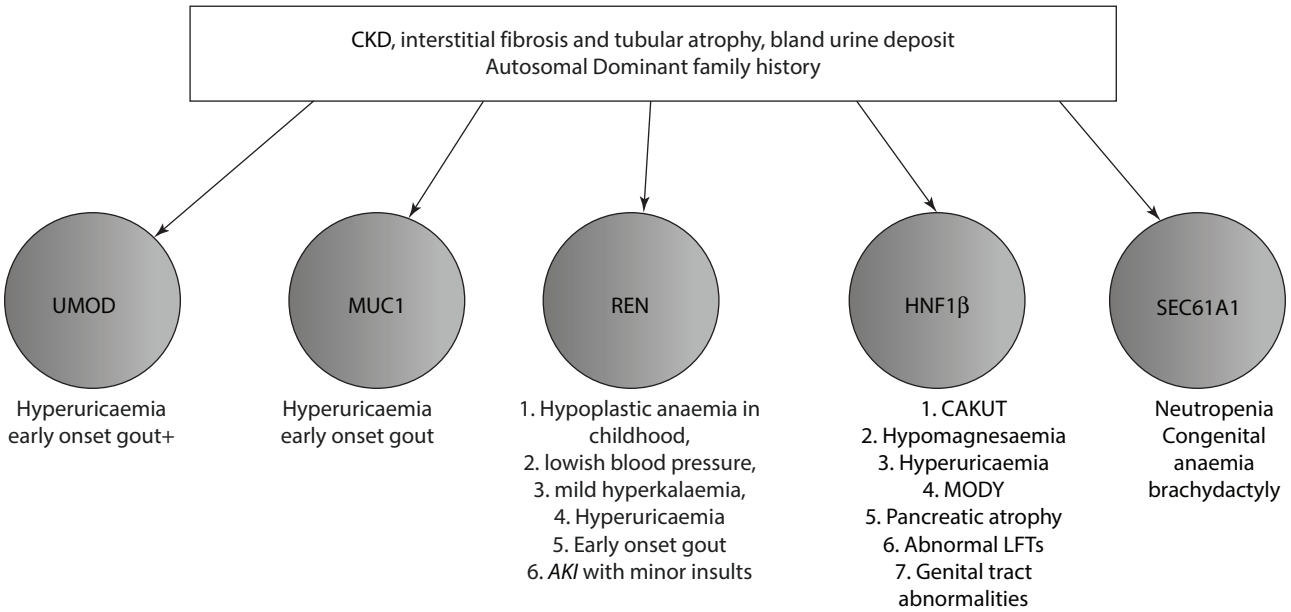


**Fig. 34.1** Genes associated with ADTKD and associated clinical features. All are associated with CKD, minimal proteinuria/bland urine and an autosomal dominant family history, although the phenotype may vary significantly in *NHF1-β* so as to appear unrelated kidney conditions. CAKUT congenital abnormalities of the kidney and urinary tract, MODY maturity-onset diabetes of the young

### 34.3.2 Clinical Features

In common with all ADTKDs, the presentation of ADTKD-UMOD is usually unflamboyant, with progressive CKD, a bland urinary sediment, an absence of hypertension and a mild urinary concentration defect. Hyperuricaemia (70%) and gout (50–75%) are common. Gout tends to be early onset (mean age 21), and men are often worse affected [6]. The clinical course is very variable, but the median age of ESRD is in the mid-50s. Cysts are seen in a proportion of patients, but their absence should not be considered strong evidence against the diagnosis. As mentioned previously, this is one reason why the old name of 'medullary cystic kidney disease type 2' has been retired. In addition, the absence of early onset gout in many people with the disorder has rendered the alternative name of 'familial juvenile hyperuricaemic nephropathy' similarly unhelpful.

### 34.3.3 Diagnosis

The diagnosis is most likely to be made in the context of a family history of early onset gout and CKD consistent with autosomal dominance by a nephrologist with a high index of suspicion. The kidneys are likely to be normal in size or small and may have some cysts (without renal enlargement). Renal biopsy is not diagnostic but likely to show IFTA as the predominant feature in the context of relatively well-preserved glomeruli. Although not a standard test, it may be possible to demonstrate excess uromodulin by immunofluorescence or to demonstrate low levels of urinary uromodulin. A definitive diagnosis is likely to rely on genetic testing.

### 34.3.4 Treatment

There is no specific treatment for ADTKD-UMOD apart from normal supportive measures for progressive CKD. As with most tubulointerstitial disease, hypertension is not a major feature and diuretics may exacerbate hyperuricaemia. Management of hyperuricaemia with xanthine oxidase inhibitors makes sense in controlling gout, although there is no data to suggest that it slows progression. Uricosurics such as benzbromarone or losartan (but probably not salicylic acid) might also be helpful. Renal transplantation is curative (with disease recurrence in an allograft not described), but potential familial live donors need genetic screening to exclude the diagnosis.

## 34.4 ADTKD-MUC1

ADTKD-MUC1 results from a mutation in the *MUC1* gene that encodes the membrane-bound mucoprotein Mucin-1 [10]. The result is progressive chronic kidney disease in the context of bland urinary sediment. It is a rare condition, although recent data suggests a prevalence similar to that of ADTKD-UMOD.

### 34.4.1 Aetiology and Pathogenesis

Mucin-1 is a membrane-bound mucoprotein found on the apical surface of epithelial cells in many tissues including reproductive organs, glandular tissue and the renal tubules. The protein has an extracellular domain, which includes a variable number of Mucin repeats, a transmembrane domain and a cytoplasmic tail that can undergo phosphorylation mediating several intracellular processes. Its functions include promoting cell growth and survival as well as preventing pathogen invasion of the cell [8].

In ADTKD-MUC1, there is a single cytosine adenine insertion in the variable number tandem repeat which encodes the extracellular Mucin repeat part of the protein. The aberrant protein Mucin-1–frameshifted (MUC1-fs) is unable to serve its intended protective function and accumulates in the cytoplasm leading to premature cell death [9]. This causes progressive nephron loss and therefore chronic kidney disease. Interestingly, in ADTKD-MUC1, this effect is isolated to renal tubular cells and not seen in other tissues.



### 34.4.2 Clinical Features

ADTKD-MUC1 is notable for its lack of distinctive characteristics [10], and this almost certainly contributes to a relatively late age of initial diagnosis (40 years). Individuals present with an elevated serum creatinine and bland urinary sediment in the context of a family history of autosomal dominant kidney disease. Hyperuricaemia and gout do occur but to a lesser degree than in ADTKD-UMOD, and again renal cysts are sometimes observed in affected individuals (hence the older name of medullary cystic kidney disease type 1 that has now fallen out of use). However, they do not have any other biochemical or imaging abnormalities to point towards a specific diagnosis. The kidneys are normal or small in size depending on the degree of chronic kidney disease. Biopsy findings are also non-specific with features of interstitial fibrosis, tubular atrophy and vasculopathy with minimal inflammation. While the mutations demonstrate complete penetrance, the age of progression to end-stage renal failure varies widely from 20 to 60 years (average 51) [7].

### 34.4.3 Diagnosis

There needs to be a high suspicion of a diagnosis of ADTKD-MUC1 in an individual with progressive CKD and a family history of autosomal dominant kidney disease in the absence of significant cystic disease on imaging [7]. However, genetic testing showing a heterozygous mutation in the *MUC1* sequence is currently the best way to confirm a diagnosis [8].

### 34.4.4 Treatment

The management of ADTKD-MUC1 is based around preventing the sequelae of CKD. Maintaining adequate hydration and avoiding nephrotoxic medications are also important. If an individual progresses to end-stage renal failure, transplantation is a curative intervention and good outcomes have been reported in this patient group. Given the mode of inheritance and variable age of development of CKD, family members who come forward for live donor transplantation should undergo genetic testing to determine their status.

## 34.5 ADTKD-REN

ADTKD-REN is a rare but interesting group of diseases resulting from mutations in the renin gene leading to progressive CKD with a bland urinary sediment. There are some clinical features that make it more distinguishable.

### 34.5.1 Aetiology and Pathogenesis

These conditions result from mutations in either the renin promoter, prosegment or mature renin peptide. Renin is expressed throughout the renal tubule and juxtaglomerular apparatus. In normal circumstances, preprorenin is translocated to the endoplasmic reticulum where it is cleaved to form prorenin and some is translocated to the lysozyme and cleaved to form active renin. Mutations of the promoter and prosegment lead to failure of normal translocation and processing, resulting in reduced functional renin and an accumulation of mutated peptide in the ER. This stresses the ER causing apoptosis, premature cell death and ultimately CKD.

Patients with mutations solely affecting the mature renin peptide probably avoid or incur less cell death from deposition of abnormal peptide but will share the characteristics of a low renin state.

### 34.5.2 Clinical Features

Reduced renin levels result in clinical features that may give useful diagnostic clues. An early feature is mild to moderate anaemia which is hypoproliferative and associated with low erythropoietin levels. This may present

in the second year of life and if apparent in the context of CKD tends to be out of proportion with eGFR. The anaemia may improve or disappear in adolescence secondary to the increase in sex hormones. The hyporeninaemic state results in a lowish blood pressure and a propensity for pre-renal AKI with relatively mild insults or a disproportionate drop in eGFR with NSAIDs. Patients tend to have mildly elevated serum potassium levels. They may also have hyperuricaemia and therefore can present with gout. Patients with mutations involving the renin promoter or prorenin segment tend to have slowly progressive CKD, reaching end-stage renal failure at an average age of 52, w hereas those with abnormalities of the mature renin peptide are more likely to present earlier with gout in their 20s with a greater range of age at the time of development of end-stage renal disease (median age of 64).

### 34.5.3 Diagnosis

Unexplained childhood anaemia, episodes of unexpected AKI, mild hypotension, mild hyperkalaemia and gout early in life are all suggestive and should be enquired about particularly in the context of reduced eGFR and a family history. These features, although subtle, should give a pretty high index of suspicion, but the definitive diagnosis is through genetic testing as biopsy findings are non-specific but may show IFTA in the context of normal glomeruli.

### 34.5.4 Treatment

Protecting the patient's intravascular volume by avoiding a low-salt diet makes sense, and fludrocortisone is helpful in maintaining intravascular volume. Theoretically, fludrocortisone will have a negative feedback on renin production and therefore slow injury to tubules from denatured proteins, although to date clinical benefit has not been proven. Patients should also avoid NSAIDs and volume depletion and may benefit from uric acid reduction with xanthine oxidase inhibitors. Transplantation is curative.

## 34.6 ADTKD-HNF1B

Mutations of the *HNF1B* gene, which encodes Hepatocyte Nuclear Factor-1-β, are associated with renal disease in two main ways: (a) via a variety of congenital abnormalities of the kidney and urinary tract (CAKUT) and tubular development and (b) later in life with ADTKD, fibrosis and tubular atrophy presenting as slowly progressive CKD. *HNF1B* mutations are also associated with extra-renal manifestations including maturity-onset diabetes of the young (MODY), abnormal liver function tests and genital tract abnormalities.

### 34.6.1 Aetiology and Pathophysiology

How *HNF1B* mutations result in adult renal disease has not been fully elucidated but includes abnormal epithelial-mesenchymal transformation, aberrant TGF-β expression and mitochondrial disease [11].

### 34.6.2 Clinical Features

Despite the autosomal dominant inheritance of *NHF1-β* mutations, the diagnosis is often difficult as there can be a large variation in clinical presentation. Even within one family, individuals can present with seemingly isolated developmental abnormalities of the kidney and urinary tract. Renal manifestations in adulthood include CKD minimal proteinuria, hypomagnesaemia and renal cystic change that can result in renal enlargement (in which situation patients may be misdiagnosed with the far more common autosomal dominant polycystic kidney disease).

Extra-renal manifestations that are helpful in raising the diagnosis are MODY (initially non-insulin-dependent diabetes before 25 years) with CT findings of pancreatic atrophy. Unexplained raised liver function tests are relatively common, and some patients may have early hyperparathyroidism and autism or develop chromophobe renal cell carcinoma. Ultrasound scans of older children with *NHF1-β* suggest that abnormal corticomedullary differentiation is common (78%) is are hyper-echoic kidneys (50%), with subcortical cysts detectable in 70% and around a third of kidneys small at presentation (REF). However, this represents patients scanned at an early age presumably because of some aspect of presentation or family history. Findings may be less clear in those patients destined to develop ESRD in late adulthood.

### 34.6.3 Diagnosis

The diagnosis may be suggested by the family history, a low magnesium or high uric acid level, although none of this is pathognomonic. MODY is an important clue, and a review of an abdominal CT specifically for pancreatic atrophy might be indicative as might be persistently abnormal liver function tests with normal synthetic function and no alternative explanation or

genital abnormalities. Renal biopsy is likely to show disproportionate IFTA but relatively preserved glomeruli which should raise ADTKD as a diagnosis but is not diagnostic. The definitive diagnosis is based on genetic testing.

### 34.6.4 Treatment

There is no specific treatment for ADTKD-*NHF1-β* mutations, but it makes sense to educate and support the patient in avoiding obesity and avoiding drugs that are diabetogenic. Transplantation is curative for renal manifestations but with a presumably high risk of NODAT in patients with pancreatic atrophy treated with CNIs and steroids.

## 34.7 Rarer Forms of ADTKD

There are a small number of rare pedigrees described with other mutations resulting in tubulointerstitial kidney disease. Mutations of the alpha-subunit of *SEC61* have been shown to be associated with abnormal translocation through the ER and accumulation of abnormal SEC61 in the tubular epithelial cells. These mutations are associated with a rare phenotype of small kidneys, simple cysts and neutropenia.

### 34.7.1 Mitochondrial Cytopathy-Related Interstitial Renal Disease

Until now, the most common presentation of mitochondrial DNA diseases involving the kidney has been Fanconi syndrome with case reports of FSGS and steroid-resistant nephrotic syndrome. However, a study of a large pedigree of maternal inherited tubulointerstitial disease recently identified a mutation causing functional impairment of mitochondrial tRNA. The phenotype was not associated with Fanconi syndrome or any systemic neurological deficit. Given the huge metabolic workload of the kidney and the relatively subtle presentation of this form of mitochondrial disorder, it would not be surprising if further mitochondrial mutations are found to result in tubulointerstitial disease. The biggest diagnostic clue here was maternal transmission [12].

### 34.7.2 Nephronophthisis

Nephronophthisis is a heterogeneous (and expanding) group of ciliopathies with autosomal recessive inheritance that are important because they are the commonest cause of ESRD in the first three decades of life (Fig. 34.2). They are, not infrequently, associated with extra-renal manifestations that result in significant disability. The proteins encoded by NPHP 1-13 are all expressed either in the primary cilia, the centrosome or basal bodies at the base of cilia in renal epithelial cells. This may result predominantly in renal disease or in a proportion of patients serious extra-renal consequences and responsible for a growing variety of clinical manifestations such as Joubert, Jeune, Meckel-Gruber and Bardet-Biedl syndromes with tapetoretinal degeneration (retinitis pigmentosa) and progressive blindness a common feature (20%). The understanding of the mutations causing these diseases is improving rapidly and is comprehensively reviewed by Devlin and Sayer [13].

The commonest (comprising 20%) of the nephronophthisis is NPHP-1 and ranges from 1:10,000 live births in Finland to 1:50,000 in Canada but seemingly less common elsewhere. As a group, they are responsible for between 2% and 15% of ESRD in children and usually diagnosed early in life.

### 34.7.3 Aetiology and Pathophysiology

As with ADTKD, a variety of genetic mutations result in a common pathway of renal epithelial cell disease. In nephronophthisis, the common pathway is via ciliary dysfunction. NPHP mutations impair intracellular signalling resulting in dysregulated tissue growth and development of cysts. Histology demonstrates interstitial fibrosis and atrophy, tubular cysts, thickened/multilayered basement membranes, relatively well-preserved glomeruli (although secondary atrophy occurs with progression) and with limited inflammation [14].

### 34.7.4 Clinical Features

The clinical features are somewhat heterogeneous depending on the mutations involved and severity of renal dysfunction. Urinary concentration disorder may be an early symptom with polyuria and polydipsia. Renal dysfunction is usually associated with normotension (perhaps not with NPHP-2) and a bland urine and normal or small kidneys on ultrasound. Cysts may be apparent but they are usually small. Retinitis pigmentosa typically presents with loss of night vision and then progressive visual loss. Those with other extra-renal manifestations may present very early with learning difficulties and cerebellar, hepatic, ocular or psychomotor signs. The key features of some eponymous syndromes linked with NPHP are shown in Table 34.1.

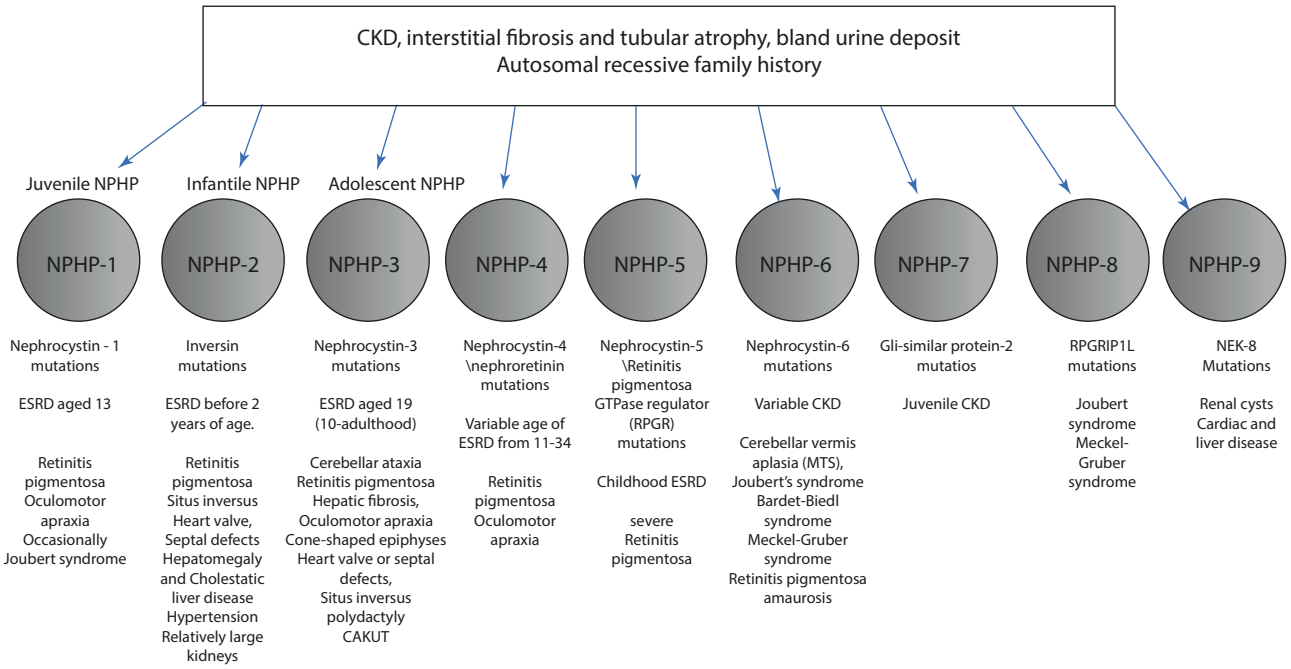


**Fig. 34.2** Characteristics of the first nine NPHPs demonstrating common themes in terms of CKD and extra-renal manifestations including Senior-Loken syndrome (combination of NPHP and retinitis pigmentosa (20%)). MTS molar tooth sign, CAKUT congenital abnormalities of the kidney and urinary tract, ESRD end-stage renal disease

**Table 34.1** Eponymous Nephronophthisis and their extra-renal manifestations

| | |
|---|---|
| Senior-Loken syndrome | Retinitis pigmentosa |
| Leber's congenital amaurosis | Retinal dystrophy |
| Joubert syndrome | Hypotonia, developmental delay, ataxia, hyperpnoea and sleep apnoea, polydactyly, low-set ears, hypertelorism, cleft lip/palate, ptosis; c haracteristic 'molar tooth sign' on MRI of the midbrain; early non-renal presentation |
| Bardet-Biedl syndrome | Obesity, retinitis pigmentosa, polydactyly and hypogonadism |
| Cogan syndrome | Ocular motor apraxia |
| Mainzer-Saldino syndrome | Cerebellar ataxia, skeletal dysplasia, retinal dystrophy |
| Jeune syndrome | Small thoracic cavity secondary to short ribs and small chest, abnormal pelvis, polydactyly; e arly non-renal presentation and short life expectancy |
| Meckel-Gruber syndrome | Pulmonary hypoplasia, occipital encephalocoele, hepatic developmental defects; l ethal in infancy |

### 34.7.5 Diagnosis

The diagnosis of NPHP is usually made by paediatricians either because of extra-renal presentation or in the context of renal impairment. The combination of retinitis pigmentosa and CKD would be highly suggestive or more extreme neurological manifestations may raise suspicion of the diagnosis alongside other clues such as situs inversus suggestive of a ciliopathy or the 'molar tooth sign' on MRI of elongated cerebellar peduncles pathognomonic of Joubert syndrome. Ultimately, neither renal imaging nor biopsy is diagnostic, and genetic screening should be undertaken.

### 34.7.6 Treatment

There is currently no treatment for the nephronophthisis beyond renal replacement therapy and, ideally, transplantation. For those patients with extra-renal manifestations, considerable thought needs to be put into coordinating long-term care and support.

### 34.7.7 Oral Facial Dactyly Syndrome

Another very rare ciliopathy associated with polycystic renal disease and hypertelorism, facial asymmetry, syn-

dactyly or polydactyly, agenesis of the corpus callosum, cleft palate or bifid tongue, missing incisors.

Mutations of the OFD-1 gene are X-linked lethal in males and usually diagnosed in females via the constellation of clinical features and confirmed by X-rays of the hand which show irregular radiolucent patches and spicules on the metacarpals and phalanges.

**Tips and Tricks**

1. The main tip is to maintain an enquiring mind when assessing a patient with unexplained CKD and, most importantly, to always take a detailed family history. This should include enquiries into consanguinity (particularly important for AR conditions), and evidence of maternal or X-linked transmission is important.
2. Checking urate levels and enquiring about early onset gout, an absence of hypertension or evidence of urinary concentration deficit, while not specific, are all suggestive of ADTKDs. Enquire about a family history of MODY, low magnesium, genital tract abnormalities for *NHF1-β* or mild hyperkalaemia, or minimally provoked AKI and childhood anaemia for REN if the possibility of ADTKD arises. Transplantation is curative for both ADTKD and nephronophthisis, but live donation needs to be accompanied with careful assessment and genetic testing of potential donors.
3. It is worth liaising with your local geneticist to agree referral criteria and for updates on conditions that can be screened for and their clinical correlates.

## 34.8 Summary

Together, the collection of diseases encompassed by nephronophthisis and ADTKD represents an important cause of ESRD. For children with nephronophthisis, this not only brings ESRD into their lives at an early stage but for some with extra-renal manifestations, additional significant disabilities. Identifying these conditions and supporting both patients and their families for the long haul, offering genetic counselling and ensuring successful transition are key aspects of care.

It is likely that many cases of ADTKD are underdiagnosed and that new mutations will be discovered for both ADTKD and nephronophthisis. As genetic screening becomes cheaper and more widely available, it should be increasingly adopted as a diagnostic tool.

**Case Study**

### Case 1

A 35-year-old man from Somalia was referred by his family doctor following blood tests to investigate fatigue, showing an eGFR of 15 ml/min. He had been separated from his family for a while and was not aware of any family history. He was normotensive and slim and his examination was unremarkable. Urine dipstick was bland and a renal ultrasound reported normal size kidneys with the appearance of CKD with reduced corticomedullary differentiation. Acute and chronic screen for secondary causes of renal failure was negative, but he had moderately raised liver function tests. A MRCP and liver screen was unremarkable. He received a deceased donor renal transplant and developed diabetes post-transplant. A review of an abdominal CT scan a few years prior demonstrated atrophy of the tail of the pancreas, and a retrospective review of pre-transplant bloods showed a low magnesium and high uric acid levels.

A presumptive diagnosis of *NHF1-β* was made and confirmed by genetic testing. Although the diagnosis had little impact for the patient, the autosomal dominant nature of the mutation had important implications for his family as well as an explanation for his abnormal liver function tests.

## Chapter Review Questions

1. What are the clinical characteristics of REN?
2. At what age do patients with NPHP 1-3 typically reach end-stage renal disease?
3. What are the functions of uromodulin (Tamm-Horsfall protein)?
4. What is cheaper, a renal biopsy or genetic testing for NPHP/ADTKD?

## Answers

1. REN is characterised by a hyporeninaemic state resulting in anaemia in childhood (hypoplastic), mild hyperkalaemia, hyperuricaemia, lowish blood pressure, AKI with minor provocation and progressive CKD with a bland urine.
2. NPHP-1, known as juvenile form, reaches ESRD at roughly 13 years; NPHP-2, known as infantile form, results in renal failure very early, typically 1 year but always before 2. NPHP-3, adolescent form, reaches ESRD at an average of 19 years but ranging from 10 to adulthood.
3. It has roles inhibiting stone formation, urinary tract infection, innate immunity, immune regulation and water regulation by the kidney.
4. A bit depends on the local costs of genetic screening, but genetic screening, if not already cheaper (and less invasive), is likely to become much cheaper than a renal biopsy.

**Acknowledgements** Acknowledgement to Professor D Gale for advice and comments.

## References

1. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management – a KDIGO consensus report. Kidney Int. 2015;88:676–83.
2. Devuyst O, Olinger E, Weber S, et al. Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers. 2019;5(1):60.
3. Cormican S, Connaughton DM, Kennedy C, et al. Autosomal dominant tubulointerstitial kidney disease (ADTKD) in Ireland. Ren Fail. 2019;41(1):832–41.
4. Devuyst O, Olinger E, Rampoldi L. Uromodulin: from physiology to rare and complex kidney disorders. Nat Rev Nephrol. 2017;13:525–44.
5. Gast C, Marinaki A, Arenas-Hernandez M, et al. Autosomal dominant tubulointerstitial kidney disease UMOD is the most frequent non polycystic genetic kidney disease. BMC Nephrol. 2018;19:301.
6. Bollée G, Dahan K, Flamant M, et al. Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. Clin J Am Soc Nephrol. 2011;6:2429–38.
7. Bleyer AJ, Kmoch S. Autosomal dominant tubulointerstitial kidney disease, MUC1-related. 2013 Aug 15 [updated 2016 Jun 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 1993–2020.
8. Gale DP, Kleta R. *MUC1* makes me miserable. J Am Soc Nephrol. 2018;29(9):2257–8.
9. Dvela-Levitt M, Kost-Alimova M, Emani M, et al. Small molecule targets TMED9 and promotes lysosomal degradation to reverse proteinopathy. Cell. 2019;178(3):521–535.e23.
10. Knaup KX, Hackenbeck T, Popp B, et al. Biallelic expression of Mucin-1 in autosomal dominant tubulointerstitial kidney disease: implications for nongenetic disease recognition. J Am Soc Nephrol. 2018;29(9):2298–309.
11. Chan SC, Zhang Y, Shao A, et al. Mechanism of fibrosis in *HNF1B*-related autosomal dominant tubulointerstitial kidney disease. J Am Soc Nephrol. 2018;29(10):2493–509.
12. Connor TM, Hoer S, Mallett A, Gale DP, Gomez-Duran A, et al. Mutations in mitochondrial DNA causing tubulointerstitial kidney disease. PLoS Genet. 2017;13(3):e1006620.
13. Devlin LA, Sayer JA. Renal ciliopathies. Curr Opin Genet Dev. 2019;56:49–60.
14. Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: disease mechanisms of a ciliopathy. J Am Soc Nephrol. 2008;20(1):23–35.

## Patient Information Websites

Autosomal dominant tubulointerstitial kidney disease (ADTKD): https://rarerenal.org/patient-information/adtkd-patient-information/

Nephronophthisis (NPHP): https://rarerenal.org/patient-information/nphp-patient-information/