Hereditary interstitial kidney disease: known genes and opportunities for diagnosis

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Abstract

Introduction

Inherited forms of tubulointerstitial kidney disease with an autosomal dominant pattern cause slowly progressive renal failure, often leading to end-stage renal disease. The diagnosis may be missed as there are limited renal and extrarenal phenotypes. Typically, the urine is inactive, with normal or small kidneys on renal ultrasounds and sometimes small cortical or corticomedullary cyst formation. Extrarenal phenotypes may include childhood anaemia and gout, out of keeping with the degree of renal failure. In order to make a diagnosis, a detailed family history and a high index of suspicion is essential.

Genetic screening for mutations in MUC1, UMOD and REN will allow a precise diagnosis to be made, allowing screening of at-risk cases and aid transplantation decisions. This review discusses known genes and opportunities for diagnosis in hereditary kidney disease.

Conclusion

We discuss the phenotypes common to all forms of autosomal dominant hereditary interstitial kidney disease and outline the key features that may help to refine a precise clinical and molecular diagnosis.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

MCKD1

The clinical phenotype of patients with MCKD1 includes slowly progressive renal failure in an autosomal dominant pattern. The age of onset of chronic kidney disease varies between families and within families, and the rate of progression is not precisely known; but the typical age of end-stage renal disease (ESRD) is 50 years of age5,6. Gout may occur, but it is not a particularly prominent phenotype. Urine is usually bland; if proteinuria is present it is typically in the subnephrotic range. Renal ultrasound may identify renal cysts, but these are not essential for diagnosis. Renal biopsy findings reveal a focal global sclerosis of glomeruli and tubular atrophy with interstitial fibrosis6.

The most important investigation is a detailed family history, in order to establish whether an autosomal dominant pattern of renal disease is present. MCKD1 patients historically were those that demonstrated linkage to a disease locus on chromosome 1q21.3,7,8. This gene locus of ~2 Mb, containing numerous genes, has taken over 10 years to solve.

However, after this long and exhaustive search of the locus, a gene that was missed by massively parallel sequencing approaches has now been identified. In a landmark study, Kirby et al. detail how, in six families, using cloning, resequencing and de novo assembly, they found mutations (single cytosine insertions) in one allele of the large variable-number tandem repeat (VNTR) sequence in the MUC1 gene9.

The clinical presentation in these families was very similar, with urinalysis revealing minimal proteinuria only; renal biopsies were available showed tubulointerstitial fibrosis and cortical (rather than medullary) renal cysts were found only occasionally. Renal ultrasound scanning also revealed small echogenic kidneys. The age of renal failure in these families ranged from 25 to 79 years10.

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The MUC1 gene encodes the protein mucin-1, which is a widely expressed protein, localized on the surface of epithelial cells. The protein contains a heavily glycosylated extracellular domain containing the VNTR11 and a self-cleavage module to allow the release of the extracellular domain15. The insertion mutation is predicted to cause a frameshift mutation, which disrupts the cleavage module and causes retention of the protein in the loop of Henle, distal convoluted tubule and the collecting ducts16. Developmental studies have shown that MUC1 is expressed in the human kidney during nephrogenesis including in the cap mesenchymal cells undergoing mesenchymal to epithelia transition, the ureteric bud tips and the collecting tubules as well as in the renal vesicles, comma bodies and S-shaped bodies. There was no glomerular expression of MUC113. These data implicate MUC1 as a key player in human renal development.

Kirby et al., in addition to the six index families, performed a genotyping screen of 21 additional unsolved families. Thirteen of these had a MUC1 mutation, suggesting that MUC1 mutation screening will be a fruitful way of solving such families19. Widespread use of such genotyping for the first time will allow a precise diagnosis to be made in families linked to chromosome 1q21, screening of other family members and also allow the diagnosis of sporadic cases. The ability to identify a disease-causing mutation also allows diagnostic workup for living-related transplantation to be more precise.

Whilst testing is not yet available in routine genetic testing laboratories, we anticipate that dedicated renal genetics research laboratories will offer genetic testing for MUC1 once a streamlined approach for analysis has been devised.

MCKD2
The clinical presentation of MCKD2 is not hugely different to that of MCKD1, with insidious loss of renal function over time and a bland urine. A key feature, however, is the incidence of gout that occurs in around half of cases and may commence early, during the second decade of life4. ESRD occurs typically between the fourth and sixth decades of life, somewhat earlier than MCKD1, but again intra- and inter-familial variability is seen. Occasionally, it may be present in children less than 10 years of age14. Renal ultrasound may reveal small kidneys and occasional medullary cysts15. Histologically, there is a diffuse tubulointerstitial fibrosis and tubular atrophy15, and uric acid crystals are not seen16.

Mutations in the gene UMOD, which encodes the urinary protein uromodulin (formerly known as Tamm–Horsfall protein), underlie MCKD2. Interestingly, uromodulin, like mucin-1, is also a mucoprotein17, although its expression pattern seems to be restricted to the thick ascending limbs (TALs) of the loop of Henle18. Like mucin-1, uromodulin is a glycosylated protein that is expressed on the apical surface of epithelial cells and is released into the urine following proteolytic cleavage19. The biological function of uromodulin has recently been reviewed20. Intriguingly, like many of the nephrocystin proteins, uromodulin may play a role in the primary cilium where it has been shown to colocalize with nephrocystin-121.

Mutations in UMOD also account for a phenotype known as familial juvenile hyperuricaemic nephropathy (FJHN). This phenotype was first described in 1960 in a family with early-onset gout, hyperuricaemia and renal disease22. UMOD mutations may also cause features of glomerulocystic kidney disease, with marked dilatation of Bowman’s space23. Together, MCKD2 and FJHN are referred to as UAKD24.

The hyperuricaemia associated with UMOD mutations is a result of a reduced fractional excretion of uric acid and predisposes to early gout. The exact mechanisms, given the molecular defect is limited to the TAL of the loop of Henle, are not well understood. There may also be a mild urinary concentrating defect15. There are no specific treatments for UAKD, although raised serum urate can be treated with allopurinol4. Febuxostat is an alternative uric acid–lowering agent if allopurinol is not tolerated. The question remains whether lowering serum uric acid would impact upon the progression of chronic kidney disease. No randomized trials addressing this question have been published.

Mutational analysis of the UMOD gene is widely available and is a straightforward gene to screen with 11 coding exons. The majority of mutations occur in exons 4 and 5, although mutations in other exons are reported25.

REN-related kidney disease
Patients with REN-related kidney disease typically present between 20 and 30 years of age with gout and chronic kidney disease. The urine is typically bland with an absence of proteinuria and ESRD occurs usually after 40 years of age26,27.

The key distinguishing features are secondary to the renin–angiotensin pathway disturbance including hypoproliferative anaemia secondary to low erythropoietin levels that may occur as early as 12 months of age. The mechanism of anaemia is thought to be secondary to reduced levels of angiotensin, which resolves during adolescence, but it may recur with the onset of chronic kidney disease. The anaemia is responsive to erythropoietin and is similar to those of patients receiving angio-tensin-converting enzyme (ACE) inhibitors28.
Secondary to low renin levels, the blood pressure may be low and there may be hyperkalaemia. A model, where renin deficiency leads to relative aldosterone deficiency, which results in a fluid-depleted state, leading to increased proximal reabsorption of uric acid and hyperuricaemia, has been proposed.26 Consistent with this, in cases studied, the fractional excretion of uric acid was low.26

Only a handful of families with REN mutations have been reported. Zivna et al. reported two families with early-onset anaemia, hyperuricaemia and progressive renal failure.26 Two novel mutations resulting from a deletion (p.Leu16del) or an amino acid exchange (p.Leu16Arg) were identified in the signal sequence of REN. Both mutations lead to either a reduction or complete absence of prorenin and renin biosynthesis and secretion.26 A third mutation was identified (p.Cys20Arg) in another family with an autosomal dominant pattern of anaemia, polyuria, hyperuricaemia and chronic kidney disease. Functional analysis of the mutation demonstrated accumulation of non-glycosylated preprorenin in the cytoplasm, leading to ultrastructural damage of the kidney.27

In a screen of 39 families with hyperuricaemia and CKD (in whom mutations in UMOD and TCF2/HNF1b had been excluded), just one family with a novel REN mutation (c.28T > C; p.W10R) was identified. This study confirms the rarity of REN mutations, even in this cohort.29 It is also noteworthy that all the reported mutations to date also warrant that all the reported mutations to date have been found in exon 1.

The REN gene is a small gene (with 10 coding exons), and genetic testing, although not widely available, can be performed by interested academic medical centres. It is at present a rare cause of hereditary interstitial kidney disease, although its true incidence is not known.

**Cases of biallelic mutations**

Given the only very recent discovery of MUC1 mutations,10 no examples of homozygous or compound heterozygous mutations have yet been reported. For UMOD, there is a single report detailing three patients from a consanguineous Spanish family with a homozygous mutation and many other family members heterozygously affected. Here, the disease pheno-type, as expected, was more severe in homozygously affected family members, with an early onset of hyperuricaemia (8–14 years of age) and a more rapid progression to ESRD (22 years of age in one case).30 Interestingly, all three homozygously affected patients had renal cysts in comparison with none of the patients with a heterozygous UMOD mutation.30

Homozygous and compound heterozygous mutations were described in REN before the milder dominant forms of REN-related disease were identified. Patients with renal tubular dysgenesis with a severe phenotype of in utero death or perinatal death secondary to anuria and pulmonary hypoplasia were found to have biallelic mutations in REN.31 This phenotype is similar to the defects seen with the use of ACE inhibitor or angiotensin II receptor antagonists during pregnancy.32,33

**Differential diagnosis of autosomal dominant hereditary interstitial kidney disease**

It is worth remembering that mutations in TCF2 encoding the transcription factor homeobox transcription factor hepatocyte nuclear factor 1 beta (HNF1b) can have a diverse range of phenotypes including cystic kidney disease, hyperuricaemia and gout.34–36 This disorder is also known as renal cysts and diabetes (RCAD), although the presence of diabetes is variable. The pattern of inheritance is autosomal dominant and the presence of cystic kidneys, gout and a blad urine in such a patient could mimic MCKD2. Indeed, the cystic change can be so dramatic that mutations in HNF1b may also mimic autosomal dominant polycystic kidney disease (ADPKD).37

We are also beginning to understand more about the phenotypic variability of ADPKD, where hypomorphic mutations can give very mild cystic change,38 which again given its dominant pattern of inheritance could mimic MCKD. A high index of suspicion is required, and it is important for the physician to question any diagnostic label that may have been applied erroneously to a family with inherited kidney disease.

**Recognition and molecular testing**

To help identify and screen patients with hereditary interstitial kidney diseases, we suggest a simple algorithm (Figure 1). We suggest that in patients with features suggestive of autosomal dominant interstitial kidney disease, a molecular genetic approach should be taken to identify the known genetic causes of his condition.

**Conclusion**

A clinical diagnosis of autosomal dominant hereditary interstitial kidney disease should be sought in cases of familial renal failure. There may be extrarenal features such as early gout or anaemia. Mutation screening for MUC1, UMOD and REN can now be undertaken to allow a precise molecular diagnosis to be made. Only then can families with these disorders be given appropriate management targeted to the underlying genetic defect, and counselling and screening of at-risk members can proceed. It remains to be seen whether there will be families that remain unsolved despite screening the known genetic causes. If so, this will open the door...


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