Diagnosis

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Review

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.

Introduction

Hereditary interstitial kidney diseases may be classified into autosomal dominant and autosomal recessive disorders. Autosomal recessive diseases include nephronophthisis, which typically leads to end-stage renal disease in the first three decades of life[1]. Nephronophthisis is a ciliopathy and may be associated with a range of extrarenal manifestations, in keeping with the fact that the underlying gene defects are all in genes encoding primary ciliary proteins[2]. Autosomal dominant interstitial kidney diseases have been classified into various types depending on their linkage to disease loci. These include medullary cystic kidney disease type 1 (MCKD1)[3], medullary cystic kidney disease type 2 (MCKD2; also known now as uromodulin-associated kidney disease, UAKD)[4] and REN-related kidney disease[5]. We review the clinical features and the underlying molecular genetics of each of these dominant causes of interstitial kidney disease.

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Discussion

MCKD1

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.stitial fibrosis[6]. The clinical phenotype of patients with MCKD1 includes slowly pro-gressive renal failure in an autosomal dominant pattern. The age of onset of chronic kidney disease varies be-tween 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 age[6,7]. 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 ul-trasound may identify renal cysts, but these are not essential for diag-nosis. Renal biopsy findings reveal a focal global sclerosis of glomeruli and tubular atrophy with interstitial fibrosis[6].

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[3,7–9]. This gene locus of ~2Mb, 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* gene[10].

The clinical presentation in these families was very similar, with urinalysis revealing minimal proteinuria only; renal biopsies where 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 years[10].

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