Evidence of further genetic heterogeneity in autosomal dominant medullary cystic kidney disease

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Abstract

Background. Autosomal dominant medullary cystic kidney disease is a genetically heterogeneous nephropathy with clinical and morphological features similar to recessively inherited juvenile nephronophthisis. Recently, a second gene locus on chromosome 16p12, MCKD2, has been mapped [1] in addition to the known locus on chromosome 1q21 (MCKD1) [2]. In a previous study we have excluded linkage for three caucasian families to the MCKD1 locus [3].

Methods. Haplotype analysis was performed on 72 individuals (including 24 affected subjects), using a set of seven microsatellite markers spanning the critical region on chromosome 16p12-p13 of about 10.5 cM.

Results. We report on haplotype analysis of closely linked markers to the MCKD2 locus in the previously studied families and two additional families.

Conclusion. In all five families the association of MCKD2 with the disease was excluded by a multipoint LOD score < -2, thus suggesting the involvement of a third MCKD locus.

Keywords: autosomal dominant medullary cystic kidney disease; chronic renal failure; haplotype analysis; juvenile nephronophthisis; medullary cystic disease

Introduction

Autosomal dominant medullary cystic kidney disease (ADMCKD) is an inherited tubulointerstitial nephropathy, which shares clinicopathological features with recessively inherited familial juvenile nephronophthisis (NPH). These features include early clinical symptoms like polyuria, polydipsia, anaemia, and changes in renal histology, as there are focal interstitial fibrosis, disintegration of the tubular basement membrane, and bilateral renal cyst formation at the corticomedullary junction. Both diseases lead to end-stage renal failure. In comparison to NPH the clinical onset of ADMCKD occurs later, usually between 30 and 50 years of age. The pathophysiology of the disease is still unknown, although similar mechanisms are proposed for diseases of the nephronophthisis/medullary cystic disease complex [2]. Genetically, ADMCKD is a heterogeneous disorder with evidence of at least three different loci. The first locus (MCKD1) is localized on chromosome 1q21 and was mapped in two large Cypriot pedigrees [2,7]. A second locus (MCKD2) has been linked to chromosome 16p12 in an Italian pedigree [1]. In both studies the disease was associated with hyperuricaemia and gout. In a previous study we reported on three caucasian multiplex families unlinked to MCKD1 [3]. Here we performed linkage analysis for MCKD2 in these and two additional families.

Subjects and methods

Pedigrees of the five families are depicted in Figure 1. Affected individuals of families MCD3, MCD4, MCD5, and MCD9 were diagnosed with ADMCKD according to criteria described previously [1,3], i.e. (i) pedigree compatible with autosomal dominant inheritance; (ii) defect in urine concentration ability with normal urinalysis; (iii) sonographic findings: normal or small kidney size and corticomedullary hyperechogeneity with occasional small medullary cysts (Figure 2); (iv) renal histology of at least one affected individual in each family consistent with ADMCKD, characterized by irregular thickening of the tubular basement membrane, round-cell infiltrates, tubulointerstitial fibrosis and eventually tubular cyst formation at the corticomedullary border. Families MCD4, MCD5, and MCD9 are from Germany, family MCD3 originated from Great Britain. The Taiwanese kindred MCD11 has been diagnosed and described clinically elsewhere [4]. Haplotype analysis was performed on a total of 72 individuals (including 24 affected subjects), using a set of seven microsatellite markers spanning the critical region on chromosome 16p12-p13 of about 10.5
Fig. 1. Segregation of chromosome 16 markers in the pedigrees of five ADMCKD families. Filled symbols indicate affected individuals, clear symbols either ‘unaffected’ (N) or unknown status (?). Haplotypes of seven consecutive microsatellite markers spanning the critical region on chromosome 16p12 [2] are shown as differently shaded bars. Haplotypes were generated by minimizing recombinants. Marker order: cen-D16S3060-D16S3017-D16S287-D16S499-D16S524-D16S3041-D16S3036-tel (flanking markers underlined). Paternal haplotypes are drawn to the left, maternal to the right.
Sonogram of the right kidney of patient no.18 in family MCD4 showing the typical ultrasonographic features of NPH/ADMCKD: Increased echogenicity with a density comparable to the liver, diminished corticomedullary demarcation and presence of multiple cysts at the corticomedullary junction, diameters ranging from 3 to 11 mm. Kidney size is at the lower normal range (96 mm maximum length).

The marker order was as follows: cen-D16S3060-D16S3017-D16S287-D16S499-D16S524-D16S3041-D16S3036-tel (Collins et al. [5]: http://cedar.genetics.soton.ac.uk/public-html/). Four-point LOD scores were calculated using the computer program VITESSE [6]. Since the penetrance of the disease is age dependent and since the age of onset is different between families, definition of ‘unaffected’ status (‘N’ in Figure 1) was made in the following way: at the critical age the individual had a normal serum creatinine, normal urinalysis, and no clinical symptoms of ADMCKD. The critical age was set at 55, 40, 40, and 35 years for families MCD3, MCD4, MCD5, and MCD9 respectively. Unaffected probands beyond this critical age were designated unknown status. In family MCD11 the children’s generation was found to be affected at an early age. Therefore siblings were considered ‘unaffected’ if they were asymptomatic at an age at which the probands were clearly affected [4]. Allele frequencies for polymorphic markers were assumed as equally distributed. Disease gene frequency was set at 10^{-4} [2].

Results and discussion

Haplotype analysis showed no cosegregation between the disease phenotype and the MCKD2 locus on chromosome 16p12 (Figure 1). Linkage calculations revealed multipoint LOD scores below −2 for each family separately as well as for all families taken together within the entire interval between flanking markers D16S3017 and D16S3036 (Figure 3). Thus, for these families we excluded linkage to the gene locus for MCKD2. However, it has to be taken into account, that two of the five families are small. As there is no linkage to chromosome 1q21 either (MCD3, MCD4, MCD5, see ref. [3]; MCD9, MCD11, unpublished data), both known gene loci for ADMCKD are not associated with the disease in our families, indicating the existence of at least a third locus. Since there is clinical variability between the families, the genetic heterogeneity observed in ADMCKD could be explained by different disease genes. The main interfamilial differences are age of onset, progression towards end-stage renal failure, and extrarenal symptoms. In the families we investigated, there is so far no evidence of an association with hyperuricaemia and gout, in contrast to both kindreds linked to MCKD1 and 2 [1,2,7,8]. The genes responsible for ADMCKD1 and ADMCKD2 have not been identified up to now. However, for NPH type 1, the recessive and juvenile-onset form of the NPH/medullary cystic disease complex, a gene has recently been identified. It encodes a membrane-associated intracellular protein including a SH3-domain [9]. Given the assumption that there is a common pathomechanism involved in these cystic nephropathies, comparison of positional candidate genes of different genetic regions can contribute to find transcripts that have similar functions or share a common pathophysiological pathway. A total genome search by linkage analysis is under way in the kindreds described in order to chromosomally map additional loci for ADMCKD and eventually identify candidate genes that can provide insight into the mechanisms involved in the pathogenesis of the disorder.

Acknowledgements. We wish to thank the patients and their families for their collaboration. We are also grateful to all physicians who provided us with clinical information about affected families and collected blood-samples, especially to G. A. Müller and D. Krieter, University Hospital Göttingen, Germany; C. Burton and T. Feest, Southmead Hospital Bristol, UK; A. Gal, Institute of Human Genetics, Hamburg, Germany; M. Schulze, University Hospital Hannover, Germany and J.-D. Tsai, Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan. For the reassessment
of the histopathological slides we would like to thank R. Waldherr, Heidelberg. AF was supported by a grant from the Deutsche Forschungsgemeinschaft (FU 202/3–1), and FH by a grant from the Zentrum für Klinische Forschung, Freiburg University (ZKF-A1).

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Received for publication: 23.8.99
Accepted in revised form: 2.12.99