Adult polycystic kidney disease in a kindred of West Indian origin exhibits linkage with the 3'HVR probe on chromosome 16

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Abstract

In a large pedigree of Caribbean origin with adult polycystic kidney disease, linkage has been established to the 3'HVR probe on chromosome 16. Although there are five different fathers in this pedigree, only one of whom was available for DNA analysis, the polymorphic nature of 3'HVR has enabled gene tracking to be carried out. The same allele cosegregates with the disease in every affected family member.

Adult polycystic kidney disease (APKD) is the second most common autosomal dominant disorder in Britain. It has been established since 1985 as being linked to the α globin gene cluster on chromosome 16.¹ Several studies since then have suggested that in spite of the varying age of onset and severity of the disease most families show linkage to chromosome 16.^{2,3} Recent reports have shown that in three families with clinical features indistinguishable from chromosome 16 linked APKD, there is no linkage to the α globin 3'HVR probe.⁴⁻⁶ One of the families was Italian⁴ and the other was of Sicilian origin.⁵ This raises the possibility that there may be other genetic loci in different ethnic groups. We have examined a family of Caribbean origin, to determine whether or not there is linkage to the 3'HVR probe. The disease in this family has led to renal failure between 33 and 44 years of age and in II-7 and II-9 (fig 1) first presented with proteinuria and hypertension in pregnancy.

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Methods

The probes used in the study are 24-1 (*D16S80*) from Dr Breuning of Leiden, and 3'HVR (*D16S85*) from Dr Higgs at the John Radcliffe Hospital, Oxford. These probes were labelled with ³²dCTP using a random hexanucleotide labelling kit from Amersham. DNA was extracted from whole blood using the method of Kunkel *et al*⁷ and digested with *Pvu*II and *Taq*I for use with 3'HVR and 24-1 respectively, in accordance with the manufacturer's (Anglian) instructions. DNA samples were electrophoresed on either 0.9% or 1.5% agarose gels and blotted onto Hybond-N membranes (Amersham) by the method of Southern.⁸ Two and three point linkage analyses were carried out using the LINKAGE programme.⁹

Results and discussion

The pedigree of the family is shown in fig 1. The 24-1 probe is not informative for this family, as the affected mother (I-5) is homozygous B1B1.¹⁰ Of the seven members of the pedigree with APKD, six gave blood samples for DNA analysis. The mother (I-5) was apparently homozygous when the samples were run on 0.9% agarose gels. However, good separation of two different alleles was achieved on a 1.5% agarose gel (fig 2, lane 6). All affected members who gave blood carried the 2.2 kb 3'HVR allele from the mother (lanes 1, 2, 7, 8, 9, fig 2), while the one unaffected daughter who gave DNA had inherited the other allele (lane 3, fig 2). There is one recombination event between 24-1 and 3'HVR in subject III-6, or III-8, since the phase of 24-1 and 3'HVR alleles in one of these subjects is different from that in the father.

A two point analysis was carried out for 3'HVR and PKD1 (so designated to distinguish it from the PKD2 locus unlinked to chromosome 16), using the M-LINK programme of LINKAGE. A lod score of 1.48 was generated at a recombination frequency of 0.06. This gives a likelihood of 30:1 in favour of the disease being linked to 3'HVR. Clearly the number of meioses in this pedigree are not sufficient to generate a more significant lod score, but the prior probability

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Figure 1 Family pedigree. B1 and B3 are alleles of probe 24-1.⁸ Alleles of 3'HVR are numbered (in kb).

Figure 2 Autoradiograph obtained after hybridisation with the 3'HVR probe. The DNA had been digested with *Pvu*II and electrophoresed in a 1.5% agarose gel. A total of 5 µg of DNA was loaded in each lane. Markers were run on the gel and photographed to obtain estimates of band sizes. Subjects shown on the gel are: lane (1) II-7*, (2) III-8*, (3) II-3, (4) III-3, (5) III-2, (6) I-5*, (7) II-9*, (8) II-2*, (9) III-6*. (a) is the 2.2 kb allele, (b) is the 2 kb allele. *Indicates clinically affected.

of linkage suggested by previous studies makes it highly likely that the disease in this family tracks with the PKD1 locus on chromosome 16. A further three point analysis test for heterogeneity using M-LINK gave a lod of 1.59 in favour of the order 3'HVR-PKD-24-1, as opposed to PKD-3'HVR-24-1, where the recombination distances were 0.06, 0.05, and 0.5, 0.11 respectively. Again, the likelihood against the disease locus lying outside the two markers is in the order of 30:1. Whether this family is typical of other Caribbean pedigrees remains to be seen, but it does suggest that the most common locus for APKD in other ethnic groups will again be on chromosome 16. As for the position of the locus for PKD2, it is of interest that a recent report has shown a lod score of >2.0 for the polymorphic marker YNH24 on chromosome 2p in the case of a large Danish pedigree.¹¹

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