Adult polycystic kidney disease

Adult polycystic kidney disease (APKD), inherited as an autosomal dominant, has a birth incidence of nearly 1 in 1000 and an apparent mutation rate of 6.5 to 10 × 10⁻⁵.¹ In Britain it is second only to familial hypercholesterolaemia (FH) in frequency and shares with FH the distinction of being an important Mendelian paradigm, study of which is likely to help clarify the aetiology of common and heterogeneous groups of diseases with variable severity. Indeed it is estimated that 10% of all end stage renal failure can be attributed to APKD although there is a wide range of ages of onset and great variation in severity. While the majority of people with the APKD gene will have developed kidney failure by the sixth decade, the frequency of polycystic kidney disease in randomly selected necropsies is considerably greater than the clinical prevalence rates.² There are also well documented instances of infantile presentation in APKD families (reviewed by Kääriäinen³ on page 474 of this issue). Unlike FH, in which the sex of the carrier and dietary factors are known to influence age of onset, it is not clear what determines the rate of cyst formation in APKD although the onset of symptoms may be attributable to complications (infection, hypertension, and kidney failure). APKD is a multisystem disease affecting typically the kidney and liver, but is also associated with intracranial arterial berry aneurysm and the risk of haemorrhage. The basic defect is unknown and recombinant DNA studies have once more proved their value in mapping a major gene in the absence of any biochemical clues, and may well lead at last to an understanding of the mysterious link between gene mutation and cystic abnormality.

In 1986 Reeders and colleagues⁴ showed genetic linkage between APKD and a hypervariable sequence (3’HVR) about 8 kb from the α globin gene cluster. This allowed APKD to be assigned to chromosome 16, the molecular genetics of which are reviewed by Sutherland et al⁵ on page 451. In the nine families studied by Reeders et al a maximum lod score (Z) of 25-85 at a recombination fraction 0.05 was reported. Subsequently, Reeders et al⁶ published details of a polymorphism of phosphoglycolate phosphatase (PGP) which was found to be closely linked to APKD (maximum lod score (Z) 11-61, recombination fraction=0) and the α globin cluster (Z=8.21, recombination fraction=0). Watson et al⁷ on page 457 provide further data on the linkage between APKD and PGP.

Lazarou et al⁸ on page 466 have now extended this work by studying 13 South Wales kindreds using haplotypes derived from restriction fragment length polymorphisms (RFLP) revealed by enzyme Rsal in the α globin gene, and the polyallelic PvuII polymorphism of the 3’HVR probe. Using the α globin and 3’HVR probes and constructing RFLP haplotypes, the system is remarkably polymorphic with 96% of subjects in the families being informative.

The study of Lazarou et al and the paper by Ryynanen et al⁹ on page 462 are consistent with a single locus for APKD in all the families studied, including apparently the remarkably benign and symptomless variety reported from Finland by Ryynanen et al. This is not to say that all adult polycystic kidney disease is due to one locus. The medullary type (McKusick 17400) and adult polycystic kidney disease with orofaciiodigital syndrome type 1⁰ are phenotypically and presumably genetically distinct. Similarly most cases of congenital or infantile polycystic disease are not associated with a family history of adult disease.

Reeders et al¹¹ have already used the 3’HVR probe for prenatal diagnosis and limitations due to a possible recombination frequency of 0.03 to 0.05 will soon be overcome if the hot pursuit of flanking probes and of the APKD gene itself are successful. It is likely that virtually all subjects and pregnancies at risk will be informative before too long. However, preliminary experience in Manchester suggests an ambivalent attitude of families to prenatal diagnosis for APKD. This is because some relatives at risk perceive the management of APKD as being acceptable, no doubt in part because of the support available from the genetic register staff who collaborate with the renal unit to offer expert ultrasound examination at 18 and 20 years to those at risk. Annual review thereafter of those found to be positive hopefully will allow early treatment of infection and of hypertension and optimum timing for renal allografts before the vascular system has been irretrievably damaged by uncontrolled hypertension.

Undoubtedly some young adults shown to be carriers will prefer prenatal diagnosis and this will usually have been conditioned by close observation of a relative with end stage renal failure. For such persons,
DNA prediction is complementary to ultrasound screening for carrier detection, but has the added advantage of not being age dependent. The immediate future will undoubtedly provide probes almost free from recombination and even greater informativeness allowing precise prediction and prenatal diagnosis in most families. But, in addition, as with all recently mapped genes, the aim is to sequence the gene, identify its product, hopefully understand the pathogenesis, and then perhaps design specific treatment.

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References