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REVIEW

Autosomal dominant polycystic kidney disease (ADPKD, MIM 173900, *PKD1* and *PKD2* genes, protein products known as polycystin-1 and polycystin-2)

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Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited nephropathy affecting over 1:1000 of the worldwide population. It is a systemic condition with frequent hepatic and cardiovascular manifestations in addition to the progressive development of renal cysts that eventually result in loss of renal function in the majority of affected individuals. The diagnosis of ADPKD is typically made using renal imaging despite the identification of mutations in *PKD1* and *PKD2* that account for virtually all cases. Mutations in *PKD1* are associated with more severe clinical disease and earlier onset of renal failure. Most *PKD* gene mutations are loss of function and a 'two-hit' mechanism has been demonstrated underlying focal cyst formation. The protein products of the *PKD* genes, the polycystins, form a calcium-permeable ion channel complex that regulates the cell cycle and the function of the renal primary cilium. Abnormal cilial function is now thought to be the primary defect in several types of PKD including autosomal recessive polycystic kidney disease and represents a novel and exciting mechanism underlying a range of human diseases.
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Clinical features

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited nephropathy characterised by the age-related development of bilateral, multiple renal cysts leading to nephromegaly and renal failure (Figure 1). It is typically a late onset disorder with renal failure developing in the sixth–eighth decades of life. Considerable clinical variability in the age of onset of renal failure is observed within and between families. In addition to renal cysts, cysts occur in the liver (70%) and pancreas (5–10%).[1] Cysts have also been reported in other organs such as the spleen, thyroid, arachnoid, seminal vesicles and prostate.[2] The prevalence of all cystic manifestations increases with age. The number and size of hepatic cysts is also correlated with female gender, parity and severity of the renal disease.[3] Massive polycystic liver disease, although rare, occurs predominantly in female subjects.

The main complications associated with renal cysts include renal failure, cyst infection and haemorrhage, renal stones and pain. Hepatic cysts may also be complicated by infection and haemorrhage.

Clinical predictors of more severe renal disease and progression to renal failure include male gender, early age of diagnosis, early age of diagnosis of hypertension, hepatic cysts in women, high parity, urinary tract infection, macroscopic haematuria and renal size expressed as renal volume.[4,5]

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Noncystic manifestations of ADPKD are also common. These include hypertension (70–80%), cardiac valve anomalies (25%) and intracranial vascular abnormalities including vascular aneurysms (8%). Rupture of cerebral aneurysms is a recognised complication of ADPKD resulting in substantial morbidity and mortality and occurs at a rate of ~1/2000 person years, five times higher than in the general population.[6,7] Abdominal wall hernias have also been associated with ADPKD.[8] While diverticulosis of the colon is unlikely to be associated with ADPKD, reports suggest that diverticulitis may be more severe in ADPKD patients requiring more frequent surgical intervention.[9,10]

All the main extrarenal manifestations of ADPKD reported in adults have been reported in children. Their presence correlates with the severity of the renal disease.[11,12] ADPKD may rarely present *in utero* or in the early postnatal period usually following the detection of renal cysts by detailed antenatal ultrasound scanning. In a large series of 83 cases identified from the literature, presenting *in utero* or in the early postnatal period, 43% of such cases died before 1 year of pulmonary or renal insufficiency with a substantial proportion (67%) developing hypertension at a mean age of 3 years.[13] Several cases of childhood onset end-stage renal failure (ESRF) were also identified in this group.

Diagnosis and screening

ADPKD is typically diagnosed in adults by the detection of bilaterally enlarged polycystic kidneys using trans-abdominal ultrasound scanning. This is a simple, widely available, noninvasive technique suitable for all ages. However, ADPKD in children, if detectable, may be unilateral or markedly asymmetrical leading to diagnostic difficulty and necessitating a different approach than in adults.[14] Computed tomography (CT) and magnetic resonance imaging (MRI) are also used where additional information on renal structure and function are required or where ultrasound resolution is poor such as in the obese individual. In addition to screening asymptomatic adult family members at-risk of inheriting ADPKD, individuals with renal tract symptoms or signs (children and adults) including macroscopic haematuria, loin pain, urinary infection or renal colic; early-onset hypertension; a sibling with early onset disease or a personal or family history of cerebral aneurysm, should also be offered screening.

For individuals at 50% risk of inheriting ADPKD (first-degree relatives of an affected individual) the diagnostic criteria of Ravine *et al*[15] for *PKD1*-linked families are commonly used. The presence of at least two renal cysts (unilateral or bilateral) in individuals younger than 30 years may be regarded as sufficient to establish a diagnosis; among those aged 30–59 years, the presence of at least two cysts in each kidney and among those aged 60 years and above, at least four cysts in each kidney should be required. A significant false-negative rate occurs in children estimated at 36% in children under 10 years.[16,17] However, over the age of 30 years, ADPKD is virtually excluded by a normal scan in *PKD1* and *PKD2* families.[17–19]

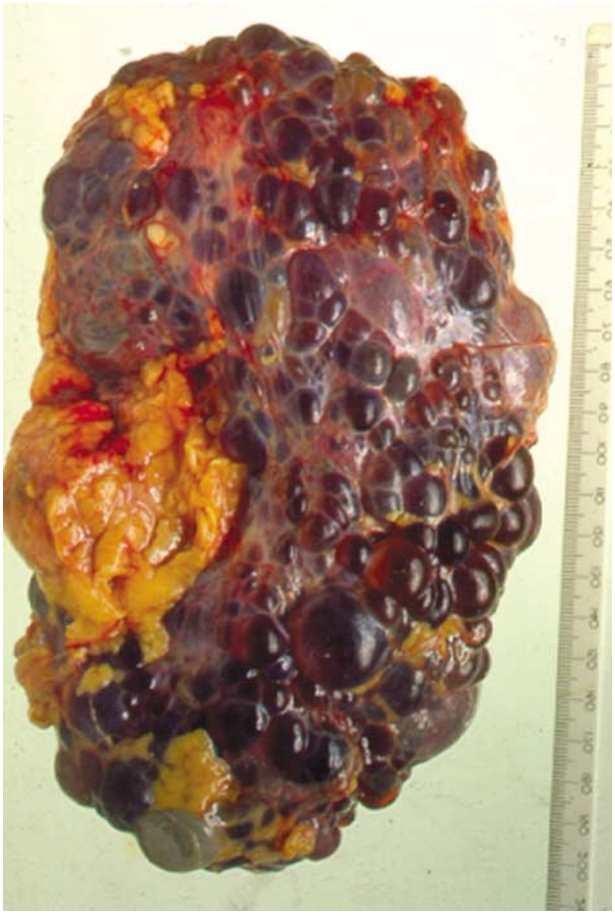

Figure 1 An explanted polycystic kidney demonstrating the massive enlargement due to multiple cysts.

Predictive or prenatal diagnosis may also be offered to ADPKD families. Predictive testing may be offered to young adults with a normal renal ultrasound who wish to clarify their disease status without waiting for further scans up to the age of 30 years. It may also be appropriate for family members wishing to act as living related kidney donors. Prenatal diagnosis is only rarely performed for this typically late-onset disease, usually in cases of the early-onset, *in utero* form, where there is considerable early morbidity and mortality and a high recurrence risk of 25% for all siblings of an affected child.[13,20,21] This high recurrence risk is not observed in more distant relatives carrying the same PKD gene mutation, suggesting the coinheritance of a modifying gene. Genetic testing is usually carried out by linkage analysis as routine clinical mutation detection services have not been established in

the majority of genetic centres worldwide, and may therefore be limited by the availability of other affected and unaffected family members. However, commercial PKD gene mutation screening (http://www.renaldx.com) has recently become available but high cost, uncertainty about mutation detection rates and the pathogenicity of missense mutations, especially in *PKD1*, may limit its clinical utility. Genetic counselling should be offered to all individuals and families with ADPKD. This will permit an informed choice to be made about diagnostic and screening tests. As ADPKD is usually a late-onset disorder, diagnosis as a young adult can have important implications. For example, a diagnosis of ADPKD can have important implications on choice of employment and provision of life, health and critical illness insurance.[22]

Differential diagnosis

Multiple renal cysts are present in a range of heritable, developmental and acquired disorders of which ADPKD is the commonest genetic cause. Acquired PKD can occur in chronic renal failure of any cause and is common in the dialysis population.[23,24] Renal size is usually reduced in contrast to ADPKD. Other polycystic kidney diseases include multicystic dysplastic kidney, autosomal recessive polycystic kidney disease, tuberous sclerosis, von Hippel–Lindau disease, nephronophthisis type 2, oro-facial digital syndrome type I and disease due to mutations in the HNF1β gene. Clinical and radiological features of these conditions should be sought and excluded in all cases of suspected ADPKD. Renal imaging should determine whether cysts are unilateral or bilateral, the cyst distribution within the kidneys, the presence of haemorrhagic and calcified renal cysts, renal size, solid renal masses, renal sinus cysts, and cysts in adjacent organs.

Disease frequency

ADPKD has been reported in all ethnic groups worldwide. It has a prevalence of approximately 1/1000 (1:400–1:1200) and is therefore one of the commonest monogenic disorders of man.[25,26] Any ethnic variation in prevalence and disease severity has not been clearly defined.[27]

Genetic heterogeneity

Mutations in *PKD1* (16p13.3) and *PKD2* (4q21–q23) account for virtually all cases of ADPKD with approximately 85% in *PKD1*. A third rare locus, *PKD3*, remains to be identified.[28]

Genes

PKD1 has 46 exons spanning 52 kb of genomic sequence and a transcript size of 14 kb, while the 5 kb *PKD2* transcript consists of 15 exons and covers 68 kb of genomic DNA.[29–31] Both *PKD1* and *PKD2* are ubiquitously expressed and are part of the polycystin gene family, which also includes *PKDREJ*, *PKD1L1*, *PKD1L2*, *PKD1L3*, *PKD2L* and *PKD2L2*.[32–36] In addition, six *PKD1* pseudogenes with ~95% homology to *PKD1* lie more proximal on chromosome 16.[37] As a consequence, only 3.5 kb of the *PKD1* transcript is single copy, which has made mutation detection difficult. Mutations in *PKD2* cause a milder phenotype with an average age of ESRF of 69 years compared to 53 years for *PKD1* mutations.[38]

Mutations

A complete mutational analysis of the *PKD1* and *PKD2* genes with a detection rate of approximately 76% has now been achieved using conventional and long-range PCR.[39,40] The majority of mutations are nonsense or frameshifting and predict a truncated protein product (see Table 1 for details of mutations identified).[41,42] Although large deletions of *PKD1* are described the frequency of this type of mutation is not known. A contiguous gene syndrome involving deletions of *PKD1* and *TSC2* has also been described where patients develop severe early-onset PKD with ESRF in childhood.[43]

In the *PKD1* gene, the location of the mutation appears to influence the disease severity with mutations in the 5′ portion of the gene (0–7812 nt) associated with a lower

Table 1 Details of mutations identified

Gene	*Loci*	*Exons*	*Gene frequency (%)*	*Mutation*	*Frequency (%)*
PKD1	16p13.3	46 (14.1 kb)	85	Nonsense	33
				Frameshifting	28
				Inframe	6
				Splicing	14
				Missense	19
PKD2	4q21–q23	15 (5 kb)	15	Nonsense	37
				Frameshifting	39
				Splicing	17
				Missense	6
				Gene deletion	1

The figures given under the title frequency are taken from Rosetti *et al*[41] and Magistroni *et al*[42] and refer to the percentage of pedigrees with known mutations.

mean age of ESRF than those 3′ of 7812 nt.[44] In addition, it has been shown that a population of *PKD1* patients presenting with a vascular phenotype have a median position of mutation located more 5′ than a control population.[45] However, the widespread variation in clinical disease severity, especially the age of onset of renal failure, both within and between families, may be due to additional, as yet unidentified, genetic and environmental modifying factors.[42,44] This clearly makes prediction of disease severity from knowledge of the mutation alone very difficult.

Germline and somatic mutations in *PKD1* and *PKD2* (including loss of heterozygosity) have been identified in cystic epithelia.[46–48] This and support from gene targeting experiments in mice (see below) suggest a 'two-hit' model of cyst formation and provide an explanation for the focal nature of the disease.

Protein function

PKD1 encodes polycystin-1, a 4302-aa, 11 transmembrane domain protein with a large extracellular region and a short cytoplasmic C-terminal tail.[30,49] *PKD2* encodes polycystin-2, a 968-aa protein, with homology to members of the transient receptor potential (TRP) superfamily of Ca^{2+} permeable cation channels.[31] Channel activation studies in a number of different cell systems have shown that polycystin-2 can act as a Ca^{2+} permeable nonselective cation channel and is regulated by polycystin-1.[50–55] Further, it has been demonstrated that polycystin-1 and -2 form a complex via an interaction between their C-termini and colocalise in the primary cilium of renal epithelial cells.[56,57] They are both required for a mechanotransduction pathway, where flow stress on the primary cilia leads to an intracellular Ca^{2+} signalling response.[58] Fibrocystin and inversin (associated with ARPKD and nephronophthisis type 2 respectively) also colocalise to the primary cilium, while OFD1 (associated with oro-facial digital syndrome type I) localises to the centrosome, at the base of the primary cilium.[59–61] Abnormal cilial function is therefore a novel pathological mechanism in renal cyst formation.

Additionally, it has been shown that polycystin-1 is involved in cell cycle regulation via the JAK-STAT signalling pathway and in G-protein signalling via the JNK/AP1 pathway suggesting additional noncilial functions.[62–64]

Animal models

Targeted mutations in murine *Pkd1*[65–68] and *Pkd2*[69,70] have demonstrated that the polycystins have a major role in renal, cardiovascular, pancreatic and skeletal development. Polycystin-2 has a further role in left–right axis determination.[70] The *Pkd1*$^{(del17-21\beta geo)}$ mutant allele has been used to define the expression pattern of *Pkd1* and demonstrates widespread expression in most tissues and cell types with highest levels in vascular smooth muscle cells and cartilage.[67] In common with other cystic mouse mutations such as *cpk*, *orpk* and *inv*, *Pkd1* and *Pkd2*, mutant mice have a defect in cilial function.[71] This provides further evidence for a common mechanism underlying renal cyst formation.

Renal cyst formation is mild in adult mice heterozygous for a *Pkd1* or *Pkd2* mutation but severe in homozygous embryos occurring from E15.5 onwards. In *Pkd2* mice with an unstable mutant allele, that undergoes somatic inactivation by intragenic homologous recombination to produce a true null allele, and trans-heterozygous *Pkd1* and *Pkd2* mutant mice, cyst formation is severe. Thus identifying complete loss of function, somatic inactivation and genetic modifiers as important in cyst pathogenesis in ADPKD.[72,73]

Clinical management

There are no disease-specific therapies for any form of PKD.[74] In addition, no evidence-based guidelines on the management of ADPKD have been reported perhaps due to the very slow rate of disease progression. In ADPKD, only blood pressure control has been shown to have a favourable impact on disease progression and cardiovascular complication rate.[75,76] Monitoring of blood pressure should also be offered to at-risk relatives who have not been screened for ADPKD because of the high incidence of hypertension, even in children.[11,77] Treatment should be started at pressures over 140/90 mmHg with optimal levels of 130/85 mmHg and even 125/75 mmHg.[78] No trials have identified which antihypertensive agent is the agent of choice in ADPKD but angiotensin-converting enzyme inhibitors are the usual first-line agents and may be safer than diuretics.[79]

Patients with ADPKD are suitable for all forms of renal replacement therapy. Pre-dialysis or -transplant nephrectomy may be required for nephromegaly or recurrent sepsis. The increasing use of living related kidney donors is likely to lead to the increasing use of high-resolution imaging and molecular testing in the screening of potential donors.[80] Partial liver resection, or occasionally liver transplantation, may be performed if ADPKD is accompanied by symptomatic massive polycystic liver disease (Figure 2). Surgical intervention in ADPKD may also be indicated for the management of pain, haemorrhage and recurrent infection. Laparoscopy may have significant advantages over open surgery.[81]

In all families with ADPKD a history of intracranial aneurysm (ICA) must be sought. While routine screening for asymptomatic ICA in all ADPKD individuals is not warranted, in families with a proven case of ICA, the risk to other affected individuals is increased ($\sim$16%) and screen-

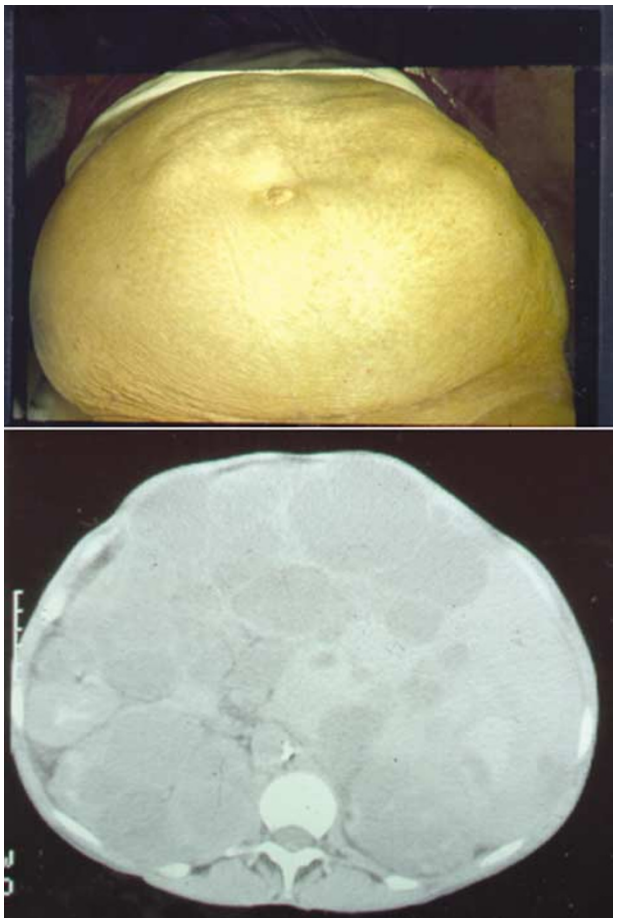

Figure 2 Abdominal distension due to polycystic liver disease in ADPKD. A CT scan demonstrates the presence of polycystic kidney disease and polycystic liver disease.

ing with magnetic resonance angiography should be considered in consultation with a neurosurgeon.[6] Periodic screening every 3–5 years has been suggested for individuals with a family history and a reasonable life expectancy. Previous rupture of an ICA is also an indication for continued screening because of the high recurrence rate (~25%).[82] For patients with positive screening for ICA, aneurysms greater than 10 mm should be considered for appropriate treatment. Periodic surveillance should be offered for smaller ICA. Given that there is considerable disagreement about the correct management of ICA, further recommendations in ADPKD will require prospective randomised trials.

All individuals with or at-risk of inheriting ADPKD should be offered genetic counselling to discuss genetic risk, screening, prenatal and predictive testing.[83] Currently in the United Kingdom, molecular diagnosis and testing is available only by linkage analysis or where a clearly pathogenic mutation has been identified as part of a research project. With the low uptake of prenatal diagnosis and the wide availability of ultrasound, CT and MR imaging the clinical indications for molecular testing are restricted to only a small number of families.

Until recently, the progression of ADPKD was followed by the development of hypertension and elevation of serum creatinine. The latter only occurs in the late stages of the disease leaving a prolonged, usually asymptomatic, period in which progression was assumed but not measured. Data now suggest that measurement of renal volumes and renal blood flow may be a useful clinical measure of progression.[84–86] The rate of change of renal volume with renal blood flow, coupled with genotype and other markers of disease severity, may allow the early identification of patients at high risk of developing renal failure in whom more aggressive treatment of blood pressure may be warranted.

Over the last three decades, mortality in ADPKD has been principally related to cardiac disease and sepsis.[87] This represents the successful introduction of renal replacement programmes over this period and highlights the need for accurate assessment and treatment of cardiovascular risk factors in this group of patients.

Recent studies using different rodent models of renal cystic diseases have suggested that various pharmacological interventions may modify disease progression. A novel tyrosine kinase inhibitor EKI-785; pioglitazone, a thiazolidinedione compound and a vasopressin V2 receptor antagonist have all been shown to beneficially modify the course of murine cystic disease.[88–90] This clearly demonstrates that a better understanding of the molecular and cellular defects underlying cystogenesis may lead to the design of novel, or the use of existing, therapeutic agents. It is therefore likely that trials in human ADPKD will be carried out in the near future, especially as methods for assessing disease progression in the short term are now available.[84,85]

Summary

ADPKD is a common and severe clinical condition leading to renal failure and cardiovascular disease in the majority of affected individuals. Mutations in *PKD1* and *PKD2* that account for virtually all cases, result in abnormal function of the renal primary cilium. This newly identified disease mechanism appears to underlie several other types of renal cystic disease including those associated with more complex developmental defects such as Bardet–Biedl syndrome.[91] Although no disease-specific therapies are currently available, the discovery of a single common pathogenic mechanism in renal cystic diseases and the identification of agents that ameliorate murine polycystic kidney disease provide valuable and exciting impetus for the search for specific pharmacological agents for the management of ADPKD.

Joint management of families with ADPKD by nephrologists and clinical geneticists will ensure the appropriate use of screening and molecular testing for at-risk individuals and may also allow the identification of individuals at high risk of developing complications such as renal failure. Clinical studies are still required to determine the utility of genotype data in the management of ADPKD; the best method for monitoring early disease progression and the most suitable antihypertensive agents. In a disease that has its main complications in later life, the slowing of progression to renal failure by only a decade could have a significant impact of morbidity and mortality.

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