

Autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease is the most prevalent, potentially lethal, monogenic disorder. It is associated with large interfamilial and intrafamilial variability, which can be explained to a large extent by its genetic heterogeneity and modifier genes. An increased understanding of the disorder's underlying genetic, molecular, and cellular mechanisms and a better appreciation of its progression and systemic manifestations have laid out the foundation for the development of clinical trials and potentially effective treatments.

Autosomal dominant polycystic kidney disease is the most common of the inherited renal cystic diseases—a group of disorders with related but distinct pathogenesis, characterised by the development of renal cysts and various extrarenal manifestations (table). In autosomal dominant polycystic kidney disease these manifestations include cysts in other organs, such as the liver, seminal vesicles, pancreas, and arachnoid membrane, and other abnormalities, such as intracranial aneurysms and dolichoectasias, aortic root dilatation and aneurysms, mitral valve prolapse, and abdominal wall hernias.

Epidemiology

Autosomal dominant polycystic kidney disease occurs worldwide and in all races. Dalgaard¹ estimated its prevalence to be one per 1000 population in Copenhagen. A study in Olmsted County, MN, USA, estimated prevalence to be between one in 400 (including observed and estimated autopsy cases) and one in 1000 (clinically diagnosed cases only).^{2,3} Lower prevalence was reported from France (one per 1111),⁴ Wales (one per 2459),⁵ and Japan (one per 4033).⁶ In the Seychelles, the prevalence in the white population was one in 544, but the disease was rare in black individuals.⁷

In the USA, around 2144 patients every year start renal replacement therapy.⁸ End-stage renal disease (ESRD) due to autosomal dominant polycystic kidney disease is less common among African Americans than among white people because of a higher incidence of ESRD from other causes in African Americans. Annual incidence rates for ESRD caused by autosomal dominant polycystic kidney disease in men and women are 8.7 and 6.9 per million (1998–2001, USA), 7.8 and 6.0 per million (1998–1999, Europe),⁹ and 5.6 and 4.0 per million (1999–2000, Japan),¹⁰ respectively. Age-adjusted sex ratios greater than unity (1.2–1.3) suggest a more progressive disease in men than in women.

Genetics

Autosomal dominant polycystic kidney disease is genetically heterogeneous with two genes identified: *PKD1* (chromosome region 16p13.3; around 85% cases) and *PKD2* (4q21; around 15% cases; figure 1).^{11–14} Whether a third gene accounts for a small number of unlinked families is uncertain. Homozygous or compound heterozygous genotypes have been thought to be lethal in utero.¹⁵ Individuals heterozygous for both *PKD1* and *PKD2*

mutations usually survive to adulthood but have more severe renal disease.^{16,17}

Several genetic mechanisms probably contribute to the phenotypic expression of the disease. Although there is evidence for a two-hit mechanism (germline and somatic inactivation of two PKD alleles) explaining the focal development of renal and hepatic cysts,^{18,19} haplo-insufficiency is more likely to account for the vascular manifestations of the disease.^{20,21} Additionally, new mouse models homozygous for *Pkd1* hypomorphic alleles^{22,23} and the demonstration of increased renal epithelial cell proliferation in *Pkd2*^{-/-} mice²⁴ suggest that mechanisms other than the two-hit hypothesis also contribute to the cystic phenotype.

The disease has large interfamilial and intrafamilial variability. Most individuals with *PKD1* mutations have renal failure by age 70 years, whereas more than 50% of individuals with *PKD2* mutations have adequate renal function at that age (mean age of onset of ESRD 54.3 years with *PKD1*; 74.0 years with *PKD2*).²⁵ Patients with mutations in the 5' region of *PKD1* have more severe disease (18.9% vs 39.7% with adequate renal function at 60 years) and are more likely to have intracranial aneurysms and aneurysm ruptures than are patients with 3' mutations.^{26,27} No clear correlations have been found with mutation type in *PKD1*, or with mutation type or position in *PKD2*.²⁸

Significant intrafamilial variability in the severity of renal and extrarenal manifestations points to genetic and environmental modifying factors. Analysis of the variability in renal function between monozygotic twins and siblings lends support to the role of genetic modifiers.²⁹ 43–78% of

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Search strategy and selection criteria

Data for this review were identified by a search of Medline and PubMed, without date restriction, for the terms “polycystic kidney disease”, “polycystic liver disease”, “autosomal dominant polycystic kidney disease”, or “autosomal dominant polycystic liver disease”. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar.

Protein		Subcellular localisation	Extrarenal manifestations
Autosomal dominant polycystic kidney disease			
<i>PKD1</i>	Polycystin 1	Primary cilium, tight junctions, adherens junctions, desmosomes, focal adhesions	Liver, seminal vesicle, pancreas, and arachnoid cysts, intracranial aneurysms, aortic root dilatation and aneurysms, mitral valve prolapse, abdominal wall hernias
<i>PKD2</i>	Polycystin 2	Primary cilium, centrosome, endoplasmic reticulum	Same as <i>PKD1</i>
Autosomal recessive polycystic kidney disease			
<i>PKHD1</i>	Fibrocystin	Primary cilium; apical membrane	Congenital hepatic fibrosis, Caroli's disease
Autosomal dominant polycystic liver disease			
<i>PRKCSH</i>	Glucosidase II β sub-unit	Endoplasmic reticulum (protein translocation machinery)	Mitral valve abnormalities, intracranial aneurysms
<i>SEC63</i>	SEC63	Same as <i>PRKCSH</i>	Same as <i>PRKCSH</i>
Tuberous sclerosis complex (autosomal dominant)			
<i>TSC1</i>	Hamartin	Cytoplasmic, microsomal and cytoskeletal compartment, tuberlin interaction	Facial angiofibromas, forehead patches, shagreen patches, subungual fibromas, hypomelanotic macules, cortical tubers, subependymal nodules, giant cell astrocytomas, cardiac rhabdomyomas, pulmonary lymphangiioleiomyomatosis
<i>TSC2</i>	Tuberlin	Cytoplasmic, microsomal and cytoskeletal compartment, interacts with polycystin 1	Same as <i>TSC1</i>
Von Hippel Lindau disease (autosomal dominant)			
<i>VHL</i>	pVHL	Cytoplasm, endoplasmic reticulum (required for ciliogenesis)	Retinal and/or central nervous system hemangioblastomas, pheochromocytomas, pancreatic cysts, and epididymal cystadenoma.
Medullary cystic kidney disease (autosomal dominant)			
<i>MCKD1</i>	Unknown	Unknown	Gout
<i>MCKD2</i>	Uromodulin	Secreted anchored protein	Gout
Nephronophthisis (autosomal recessive)			
<i>NPHP1</i>	Nephrocystin 1	Primary cilium, centrosome, adherens junctions, focal adhesions	Retinitis pigmentosa (Senior-Löken syndrome), ocular motor apraxia (Cogan syndrome), congenital hepatic fibrosis, peripheral dysostosis (cone-shaped epiphyses), truncal cerebellar ataxia
<i>NPHP2; INVS</i>	Inversin	Primary cilium, centrosome, adherens junctions	Situs inversus, ventricular septal defect
<i>NPHP3</i>	Nephrocystin 3	Primary cilium/centrosome (predicted)	Same as <i>NPHP1</i>
<i>NPHP4</i>	Nephrocystin 4	Primary cilium, centrosome, adherens junctions	Same as <i>NPHP1</i>
<i>NPHP5; IQCB1</i>	Nephrocystin 5	Primary cilium	Same as <i>NPHP1</i>
<i>NPHP6; CEP290</i>	Nephrocystin 6	Centrosome	Same as <i>NPHP1</i>

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the variance in age to ESRD could be due to heritable modifying factors.^{30,31} Parents are as likely as children to show more severe disease in studies of parent-child pairs.³²

Pathogenesis

The protein products of *PKD1* and *PKD2*, polycystin-1 (around 460 kDa)^{11,12} and polycystin-2 (around 110 kDa)³³ are membrane proteins (with 11 and six transmembrane domains, respectively) that probably form a functional complex (figure 2).^{34–38} Polycystin-2 is a non-selective cation channel capable of transporting calcium ions (Ca^{2+}).^{39–41} Polycystin-1 is probably a receptor for an unidentified ligand. Like many other proteins implicated in renal cystic diseases (table) the polycystins are located in the primary cilium,^{42,43} a single hair-like organelle projecting from the surface of most mammalian cells.^{44,45} In tubular epithelial cells the cilium projects into the lumen and is thought to have a sensory role (figure 3). *Pkd1*^{-/-} cells have normal-appearing cilia, but lack the flow-induced Ca^{2+} response noted in normal cells.^{44,46} This finding suggests that the polycystin complex acts as a mechanosensor on

cilia, detecting changes in flow, and that the Ca^{2+} influx occurs through the polycystin-2 channel. The Ca^{2+} influx in turn induces release of Ca^{2+} from intracellular stores (figures 3 and 4).

Polycystin-1 is also found in the plasma membrane at focal adhesions, desmosomes, and adherens junctions,^{47–50} whereas polycystin-2 is found in the endoplasmic reticulum (figure 3).^{51–53} Polycystin-1 in the plasma membrane may interact with polycystin-2 in the adjacent endoplasmic reticulum. Polycystin-2 physically interacts with the transient receptor potential channel 1 (TRPC1), a store-operated Ca^{2+} channel.⁵⁴ Therefore, polycystin function probably extends beyond primary cilia. Ca^{2+} release from intracellular stores in response to agonist stimulation is amplified in cells overexpressing polycystin-2⁵⁵ and is blunted in cells with a 50% reduction in either polycystin.^{20,56} Loss of polycystin-2 localisation to the mitotic spindle by knockdown of the interacting cytoskeletal protein mDia1 blunts agonist-evoked increases in intracellular concentrations of Ca^{2+} in dividing cells that lack primary cilia.⁵⁷ Intracellular concentrations of Ca^{2+} are

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Joubert syndrome (autosomal recessive)

<i>JBTS2</i>	Unknown	Unknown	Cerebellar vermis hypoplasia with abnormal superior cerebellar peduncles (molar tooth sign), mental retardation, hypotonia, irregular breathing, and eye-movement abnormalities
<i>NPHP1</i>	Nephrocystin 1	Primary cilium, centrosome, adherens junctions, focal adhesions	Same as <i>JBTS2</i>
<i>NPHP6; CEP290</i>	Nephrocystin 6	Centrosome	Same as <i>JBTS2</i>

Bardet-Biedel syndrome (autosomal recessive)

<i>BBS1</i>	BBS1 protein	Centrosome	Pigmentary retinopathy, distal limb anomalies, renal abnormalities, obesity, hypogonadism in men, and mental retardation
<i>BBS2</i>	BBS2 protein	Centrosome	Same as <i>BBS1</i>
<i>BBS3; ARL6</i>	ARL6 protein	Centrosome	Same as <i>BBS1</i>
<i>BBS4</i>	BBS4 protein	Primary cilium; centrosome	Same as <i>BBS1</i>
<i>BBS5</i>	BBS5 protein	Centrosome	Same as <i>BBS1</i>
<i>BBS6; MKKS</i>	BBS6 chaperonin	Centrosome	Same as <i>BBS1</i>
<i>BBS7</i>	BBS7 protein	Centrosome	Same as <i>BBS1</i>
<i>BBS8; TTC8</i>	TTC8 protein	Primary cilium; centrosome	Same as <i>BBS1</i>
<i>BBS9; PTHB1</i>	PTHB1 protein	Undetermined	Same as <i>BBS1</i>
<i>BBS10</i>	BBS10; C12orf58	Undetermined	Same as <i>BBS1</i>
<i>BBS11</i>	TRIM32, E3 ubiquitin ligase	Cytoskeleton	Same as <i>BBS1</i>

Meckel-Gruber syndrome (autosomal recessive)

<i>MKS1</i>	MSK1 protein	Centrosome	Occipital encephalocele, hydrocephalus, polydactyly, and fibrocystic liver disease
<i>MKS3</i>	Meckelin	Centrosome	Same as <i>MKS1</i>

Orofacial digital syndrome type 1 (X-linked)

<i>OFD1</i>	OFD1 protein	Centrosome	Oral (eg, cleft tongue or palate), facial (eg, broad nasal root) and digital abnormalities
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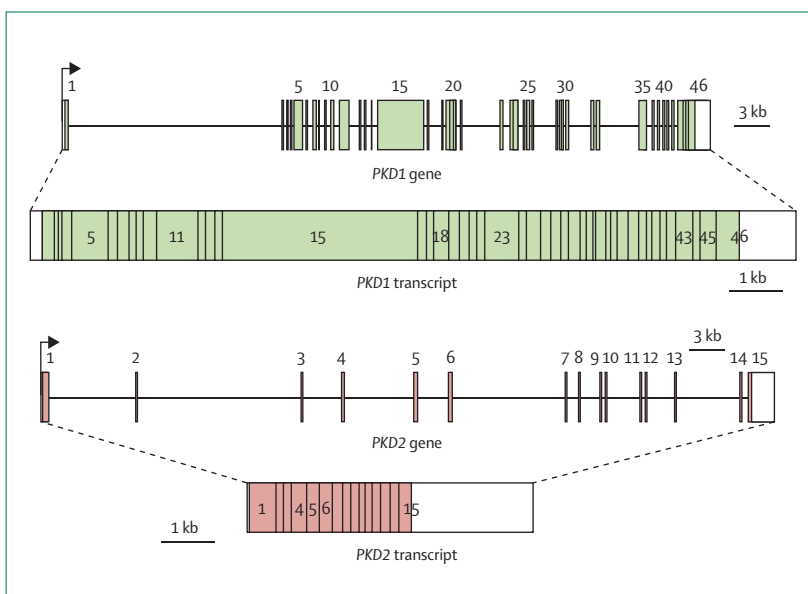
Glomerulocystic kidney disease (autosomal dominant)

<i>HNF1β</i>	HNF-1β transcription factor	Nucleus	Maturity-onset diabetes of the young (MODY), genital tract abnormalities
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Table: Inherited cystic diseases, by causal gene

reduced in cyst-derived, primary cultured cells from the kidneys of individuals with *PKD1* mutations⁵⁸ and in collecting ducts isolated from *Pkd1*^{-/-} mice.⁵⁹

Increased renal concentrations of cyclic AMP (cAMP) are common in animal models of polycystic kidney disease.⁶⁰⁻⁶² This finding could be directly related to changes in intracellular Ca²⁺ homeostasis by stimulation of Ca²⁺-inhibitable adenylyl cyclase 6 or inhibition of Ca²⁺-dependent phosphodiesterase 1 (figure 4). Concentrations of cAMP are also increased in vascular smooth-muscle cells isolated from *Pkd2*^{-/-} mice. Intracellular Ca²⁺ regulates concentrations of cAMP in both wild-type collecting duct principal cells and in vascular smooth-muscle cells.^{63,64} cAMP stimulates mitogen-activated protein kinase and extracellularly regulated kinase (MAPK/ERK) signalling and cell proliferation in renal epithelial cells of patients with polycystic kidney disease, whereas it has an inhibitory effect in wild-type cells.^{65,66} The abnormal proliferative response to cAMP is directly linked to alterations in intracellular Ca²⁺ concentration since it can be reproduced in wild-type cells by lowering the intracellular concentration of Ca²⁺.⁶⁷ Conversely, Ca²⁺ ionophores or channel activators can rescue the abnormal response of cyst-derived cells.⁵⁸

**Figure 1: PKD1 and PKD2 genes and transcripts**

The positions of the exons are shown and numbered: 46 for *PKD1* (top) and 15 for *PKD2* (bottom). The coding regions are shaded: green for *PKD1* and pink for *PKD2*; 5' and 3' untranslated regions are not shaded.

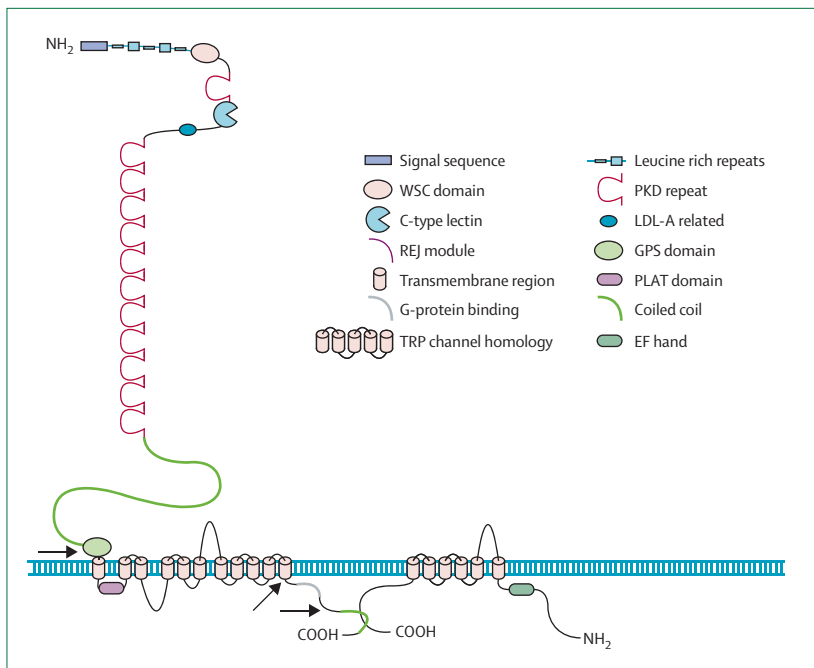


Figure 2: Polycystin-1 (left) and polycystin-2 (right) and interaction via their C-terminal tails
 Details of the domains and regions of homology are shown in the key. Recently, it has been proposed that polycystin-1 could activate transcription directly by cleavage and translocation of the C-terminus to the nucleus, a process found in other transmembrane proteins. The cleavage site in the GPS region⁶⁶ and possible cleavage sites in the C-terminal tail of polycystin-1^{37,38} are shown by arrows. WSC=cell wall integrity and stress-response component 1. REJ=receptor for egg jelly. TRP=transient receptor potential. PKD=polycystic kidney disease. LDL-A=low density lipoprotein class A. GPS=proteolytic G protein-coupled receptor proteolytic site. PLAT=polycystin, lipoxigenase, and alpha toxin.

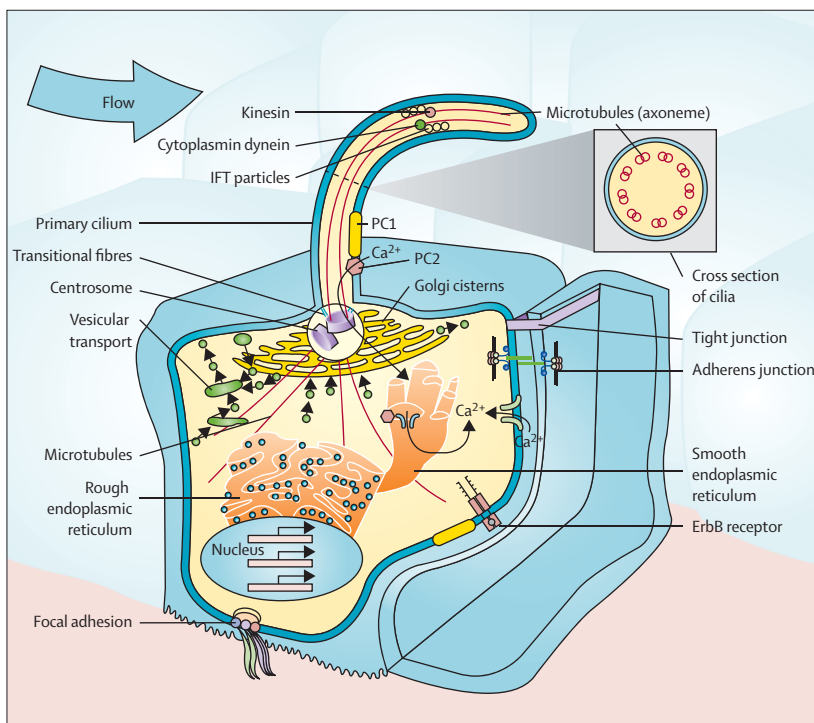


Figure 3: Schematic representation (not to scale) of a tubular epithelial cell, the primary cilium, and possible functions of the polycystins

Upregulation of the vasopressin V2 receptor and high circulating vasopressin concentrations could contribute to the increased cAMP concentrations (figure 3). Cyst-derived epithelial cells also exhibit increased expression and apical localisation of the ErbB1 (EGFR) and ErbB2 receptors.⁶⁸ Activation of these receptors by EGF-related compounds present in cyst fluid probably contributes to stimulation of MAPK/ERK signalling. ERK activation promotes G1/S phase transition and cell proliferation through regulation of cyclin D1, phosphorylation of the retinoblastoma protein by cyclin-dependent kinase (CDK) 4/6-cyclin D and CDK2-cyclin E, and release of E2F transcription factor.⁶⁹

A range of additional pathways by which extracellular cues detected by the polycystin complex might be transmitted to the nucleus have been proposed (figure 2).^{70,71} Polycystin-1 has been proposed to affect Janus kinase 2/STAT3, NFAT (nuclear factor of activated T cells), and NF-κB (nuclear factor kappa B) signalling.

Diagnosis

The diagnosis of autosomal dominant polycystic kidney disease in an individual with a positive family history relies on imaging testing. Counselling should be done before testing.⁷² Benefits of testing include certainty of diagnosis that could affect family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living related donor transplantation. Potential discrimination in terms of insurability and employment associated with a positive diagnosis should be discussed. Until effective treatments become available, the adverse effects from presymptomatic diagnosis in children (removal of choice to know or not know, psychological, educational, and career implications, and insurability issues) outweigh the benefits.

Renal ultrasonography is commonly used because of cost and safety. Sonographic diagnostic criteria for individuals at 50% risk for the disease include at least two unilateral or bilateral cysts in individuals younger than 30 years; two cysts in each kidney in individuals 30–59 years; and four cysts in each kidney in individuals 60 years or older.⁷³ The sensitivity of these criteria is nearly 100% for individuals 30 years or older and for younger individuals with *PKD1* mutations, but only 67% for individuals with *PKD2* mutations younger than 30 years.⁷⁴ For comparison, ultrasonography detects at least one cyst in 0% of healthy individuals aged 15–29 years, 1.7% of those aged 30–49 years, 11.5% of those aged 50–70 years, and 22.1% of those aged 70 years and above. Bilateral renal cysts (at least one cyst in each kidney) are detected in 1%, 4%, and 9% of those aged 30–49 years, 50–70 years, and older than 70 years, respectively.⁷⁵ Because CT and MRI are more sensitive than ultrasonography, the sonographic criteria listed above are not applicable to these techniques.

In the absence of a family history of autosomal dominant polycystic kidney disease, bilateral renal enlargement and

cysts or the presence of multiple bilateral cysts with hepatic cysts together with the absence of other manifestations suggesting a different renal cystic disease provide presumptive evidence for the diagnosis (table). In addition to the inherited diseases listed in the table, other disorders need to be considered. In acquired renal cystic disease associated with longstanding renal insufficiency, the kidneys are initially small. With time they can enlarge and resemble those of autosomal dominant polycystic kidney disease. Localised renal cystic disease, characterised by non-progressive cystic transformation of a portion of a kidney, should be differentiated from asymmetric presentations of autosomal dominant polycystic kidney disease, segmental multicystic dysplasia, and cystic neoplasms. In rare cases, medullary sponge kidney, a disorder characterised by tubular dilatation of the collecting ducts confined to the medullary pyramids, can mimic the urographic appearance of autosomal dominant polycystic kidney disease. The absence of a family history of the disease and the sparing of the cortex on CT or MRI point to the right diagnosis.

Genetic testing can be used when the imaging results are equivocal or when a definite diagnosis is required in a younger individual, such as a potential living related kidney donor. Prenatal and preimplantation genetic testing are rarely considered for autosomal dominant polycystic kidney disease.^{76,77} Genetic testing can be done by linkage or sequence analysis. Linkage analysis uses highly informative microsatellite markers flanking *PKD1* and *PKD2* and requires accurate diagnosis, availability, and willingness of sufficient affected family members to be tested. Because of these constraints, linkage analysis is suitable in fewer than 50% of families. The large size and complexity of *PKD1* and marked allelic heterogeneity are obstacles to molecular testing by direct DNA analysis. Mutation scanning by methods such as denaturing high performance liquid chromatography (DHPLC) in research settings has yielded mutation detection rates of around 65–70% for *PKD1* and *PKD2*.^{78,79} Higher rates of around 85% are now possible by direct sequencing.⁸⁰ However, because most mutations are unique and up to a third of *PKD1* changes are missense, the pathogenicity of some changes is difficult to prove.

Renal manifestations

Cyst development and growth

Many manifestations are directly related to the development and enlargement of renal cysts. A study of 241 non-azotemic patients followed up prospectively with yearly MRI examinations by the Consortium of Radiologic Imaging Studies to assess the Progression of Polycystic Kidney Disease (CRISP) has provided invaluable information to understand how the cysts develop and grow.^{81,82} Total kidney volume and cyst volumes increased exponentially. At baseline mean total kidney volume was 1060 mL and the mean increase over 3 years was 204 mL or 5–3% per year. The rates of change of total kidney and

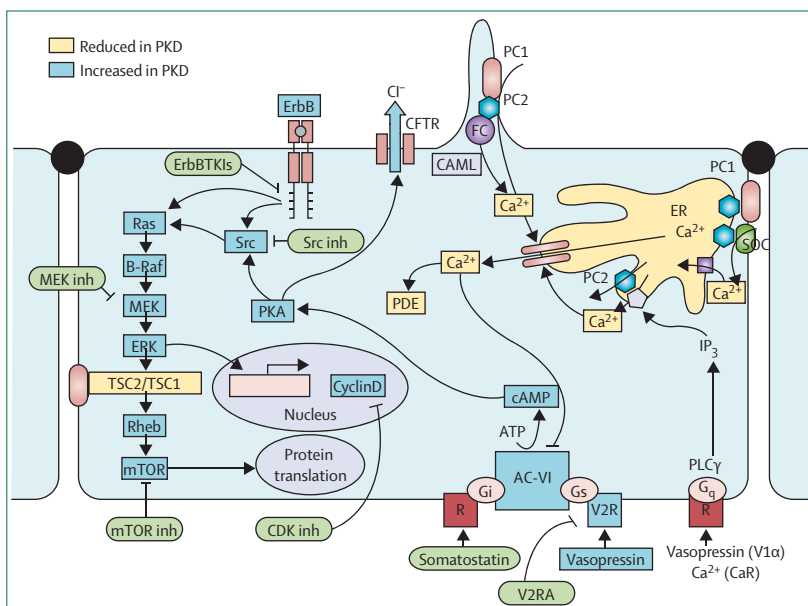


Figure 4: Hypothetical pathways up-regulated or down-regulated in polycystic kidney disease
Potential therapeutic agents for polycystic kidney disease are shown in green boxes. AC-VI=adenylyl cyclase 6. CDK=cyclin-dependent kinase. ER=endoplasmic reticulum. MAPK=mitogen-activated protein kinase. mTOR=mammalian target of sirolimus. PC1=polycystin-1. PC2=polycystin-2. PDE=phosphodiesterase. PKA=protein kinase A. R=receptor. TSC=tuberous sclerosis proteins tuberin (TSC2) and hamartin (TSC1). V2R=vasopressin V2 receptor. V2RA=vasopressin V2 receptor antagonists.

total cyst volumes, and of right and left kidney volumes, were strongly correlated. Baseline total kidney volume predicted the subsequent rate of increase in renal volume and was associated with declining glomerular filtration rate (GFR) in patients with baseline total kidney volume above 1500 mL. At baseline, *PKD1* kidneys had more cysts and were larger than *PKD2* kidneys. Although the absolute changes in kidney volume were greater for *PKD1* (74.9 mL/year) than for *PKD2* (32.2 mL/year) patients, the rates of growth were not significantly different (5.68% per year vs 4.82% per year). This result suggests that cyst initiation, but not cyst enlargement, is modulated by the disease gene. Men had higher rates of kidney and cystic expansion than women.⁸³

Early renal-function abnormalities

Impaired urinary concentrating capacity is common even at early stages.⁸⁴ 60% of children cannot maximally concentrate the urine. Plasma vasopressin concentrations are increased. The vasopressin-resistant concentrating defect is not explained by reduced cAMP or expression of concentration-associated genes, which are consistently increased in animal models. This defect is often attributed to disruption of the medullary architecture because its presence and severity correlate with the extent of the cystic disease. Nevertheless, this change precedes the cystic dilatation of collecting ducts in animal models induced by diphenylamine or diphenylthiazole, and overexpression of concentration-associated genes precedes cyst development in a genetic model. Defective translocation of aquaporin 2

to the apical membrane has been suggested in some mouse studies,⁸⁵ but not in human autosomal dominant polycystic kidney disease.

Recent studies suggest that the urinary concentrating defect and raised vasopressin concentrations could contribute to cystogenesis.^{61,62,85,86} They might also contribute to the glomerular hyperfiltration seen in children and young adults, the development of hypertension, and chronic kidney-disease progression.^{87–91} Defective medullary trapping of ammonia and transfer to the urine caused by the concentrating defect could contribute to the low urine pH values, hypocitric aciduria, and predisposition to stone formation.⁹²

Another early functional defect is a reduction in renal blood flow,^{93–95} which could be due to the development of cysts with changes in intrarenal pressures, to neurohumoral or local mediators, or to intrinsic vascular abnormalities.

Hypertension

Hypertension (blood pressure >140/90 mm Hg) is present in around 50% of patients aged 20–34 years with autosomal dominant polycystic kidney disease and normal renal function. This figure increases to nearly 100% of patients with ESRD.⁹⁶ Prevalence in children is between 5% and 44%, but is difficult to ascertain accurately because of selection biases and the different definitions of hypertension used in the studies.⁹⁷ Its development is accompanied by a reduction in renal blood flow, increased filtration fraction, abnormal renal handling of sodium, and extensive remodelling of the renal vasculature.^{94,98}

The association between renal size and prevalence of hypertension has lent support to the hypothesis that stretching and compression of the vascular tree by cyst expansion causes ischaemia and activation of the renin-angiotensin system.⁹⁹ Whether the classic, circulating, renin-angiotensin system is inappropriately activated is controversial.^{93,100} There is stronger evidence for the activation of a local intrarenal renin-angiotensin system. This includes: (1) partial reversal of the reduced renal blood flow, increased renal vascular resistance, and increased filtration fraction by acute or chronic administration of an angiotensin-converting enzyme (ACE) inhibitor;^{93–95} (2) shift of immunoreactive renin from the juxtaglomerular apparatus to the walls of the arterioles and small arteries;^{101,102} (3) ectopic synthesis of renin in the epithelium of dilated tubules and cysts;^{102,103} and (4) ACE-independent generation of angiotensin II by a chymase-like enzyme.¹⁰⁴

The expression of polycystin-1 and polycystin-2 in vascular smooth muscle^{105–107} and endothelium,¹⁰⁸ along with enhanced vascular smooth-muscle contractility¹⁰⁹ and impaired endothelial-dependent vasorelaxation,¹¹⁰ suggests that a primary disruption of polycystin function in the vasculature could also play a part in the early development of hypertension and renal vascular remodelling. Studies have shown that nitric oxide endothelium-dependent vasorelaxation is impaired in small subcutaneous resistance vessels from patients with normal renal function before

development of hypertension.^{110–112} Other factors proposed to contribute to hypertension in autosomal dominant polycystic kidney disease include increased sympathetic nerve activity, increased plasma endothelin-1 concentrations, and insulin resistance.¹¹³

The diagnosis of hypertension in autosomal dominant polycystic kidney disease is often made late. 24 h ambulatory blood pressure monitoring of children or young adults without hypertension can reveal raised blood pressures, and attenuated nocturnal blood-pressure dipping and exaggerated blood-pressure response during exercise, which can be accompanied by left ventricular hypertrophy and diastolic dysfunction.¹¹⁴ Early detection and treatment of hypertension is important because cardiovascular disease is the main cause of death and uncontrolled blood pressure increases the risk for proteinuria, haematuria, decline of renal function, and morbidity and mortality from valvular heart disease and aneurysms.^{2,115,116} The presence of hypertension increases the risk of pre-eclampsia and fetal loss.¹¹⁷ Normotensive women usually have uncomplicated pregnancies.

Pain

Pain is the most common symptom (around 60%) reported by adult patients.^{118,119} Acute pain can be associated with renal haemorrhage, passage of stones, and urinary tract infections. Some patients develop chronic flank pain without identifiable cause other than the cysts.

Vascular endothelial growth factor produced by the cystic epithelium¹²⁰ can promote angiogenesis, haemorrhage into cysts, and gross haematuria. Symptomatic episodes probably underestimate the frequency of cyst haemorrhage because more than 90% of patients with autosomal dominant polycystic kidney disease have cysts that are hyperdense (on CT) or high signal (on MRI), indicative of blood or high protein content. Most haemorrhages resolve within 2 to 7 days. If symptoms last longer than 1 week or if the initial episode occurs after the age of 50 years, investigation to exclude neoplasm should be undertaken.

About 20% of patients with autosomal dominant polycystic kidney disease have kidney stones.^{121–123} The composition of these stones is usually uric acid or calcium oxalate. Metabolic factors include decreased ammonia excretion, low urinary pH, and low urinary citrate concentration. Urinary stasis secondary to the distorted renal anatomy might also play a part. Stones can be difficult to differentiate from cyst wall and parenchymal calcification.

As in the general population, urinary tract infections affect women more commonly than men. Most infections are caused by enterobacteriaceae.¹²⁴ CT and MRI are sensitive for the detection of complicated cysts and provide anatomical definition, but the findings are not specific for infection. Nuclear imaging (67-Ga or 111-In-labelled leucocyte scans) is useful but false negative and positive results are possible. Cyst aspiration should be considered when the clinical setting and imaging are suggestive and blood and urine cultures are negative.

Renal-cell carcinoma is a rare cause of pain in autosomal dominant polycystic kidney disease. It does not occur more commonly than in the general population, but it can present at an earlier age with frequent constitutional symptoms and a higher proportion of sarcomatoid, bilateral, multicentric, and metastatic tumours.¹²⁵ A solid mass on ultrasonography, speckled calcifications on CT, and contrast enhancement, tumour thrombus, and regional lymphadenopathies on CT or MRI should raise suspicion of a carcinoma.

Renal failure

The development of renal failure is highly variable. In most patients renal function is maintained within the normal range, despite relentless growth of cysts, until the fourth to sixth decade of life. By the time renal function starts declining, the kidneys are usually substantially enlarged and distorted with little recognisable parenchyma on imaging studies. At this stage, the average rate of GFR decline is about 4·4–5·9 mL/min/year.¹²⁶ The mutated gene (*PKD1* vs *PKD2*), position of the mutation in *PKD1*, and modifier genes determine to a significant extent the clinical course of autosomal dominant polycystic kidney disease. Other risk factors include male sex (particularly in those with *PKD2* mutations), black race, first episode of haematuria before the age of 30 years, onset of hypertension before the age of 35 years, hyperlipidaemia, low HDL cholesterol concentrations, and sickle cell trait.^{127–129} Whether African-Americans or individuals with specific ACE or ENOS genotypes are at an increased risk of disease progression is uncertain. Smoking increases the risk for ESRD at least in some patient subsets (male smokers with no history of treatment with ACE inhibitors).¹³⁰

Several mechanisms account for renal function decline. CRISP has confirmed previous studies suggesting a strong link with renal enlargement^{99,131–133} and has shown that kidney and cyst volumes are the strongest predictors of renal-function decline. CRISP showed that renal-blood flow (or vascular resistance) is an independent predictor.¹³⁴ This finding points to the importance of vascular remodelling in the progression of the disease and could account for cases where the decline of renal function seems to be out of proportion to the severity of the cystic disease. Angiotensin II, transforming growth factor β , and reactive oxygen species might contribute to the vascular lesions and interstitial fibrosis by stimulating the synthesis of chemokines, extracellular matrix, and metalloproteinase inhibitors. Other factors such as heavy use of analgesics could contribute to chronic kidney disease progression in some patients.

Early onset autosomal dominant polycystic kidney disease

Rarely (<1% cases), autosomal dominant polycystic kidney disease can present in utero or in the neonatal period, similarly to autosomal recessive disease.^{135,136} In around 50% of the cases the affected parent had not been aware of the diagnosis. Additionally, de novo cases of early onset,

autosomal dominant polycystic kidney disease can occur. Rarely, molecular genetic studies suggest autosomal recessive disease, but renal or hepatic cystic disease in a parent, possibly due to coinheritance with autosomal dominant disease, point to the usefulness of molecular testing. The recurrence risk of severe, early onset, autosomal dominant polycystic kidney disease in siblings has been estimated to be 25%.

Extrarenal manifestations

Polycystic liver disease

Polycystic liver disease is the most common extrarenal manifestation. It is associated with both *PKD1* and non-*PKD1* genotypes. The disease also occurs as a genetically distinct disease in the absence of renal cysts.^{137–139} Like autosomal dominant polycystic kidney disease, autosomal dominant polycystic liver disease is genetically heterogeneous, with two genes identified (*PRKCSH* and *SEC63*), which account for around a third of isolated cases.^{140–142}

Liver cysts arise by excessive proliferation and dilatation of biliary ductules and peribiliary glands. Oestrogen receptors are expressed in the epithelium lining the hepatic cysts and oestrogens stimulate hepatic-cyst-derived cell proliferation.¹⁴³ Growth of liver cysts is also promoted by growth factors and cytokines secreted into the cyst fluid.^{144,145}

Hepatic cysts are rare in children. Their frequency increases with age and might have been underestimated by ultrasound and CT studies. Their prevalence by MRI in the CRISP study was 58% in 15–24 year olds, 85% in 25–34 year olds, and 94% in 35–46 year old participants.¹⁴⁶ Hepatic cysts are more prevalent and hepatic cyst volume is larger in women than in men. Women who have multiple pregnancies or who have used oral contraceptive drugs or oestrogen replacement therapy have worse disease, suggesting an oestrogen effect on hepatic-cyst growth.^{147,148}

Typically, polycystic liver disease is asymptomatic, but symptoms have become more common as the lifespan of patients with polycystic kidney disease has lengthened with dialysis and transplantation. Symptoms can result from mass effect or from complications related to the cysts. Symptoms typically caused by massive enlargement of the liver or by mass effect from a single or a limited number of dominant cysts include dyspnoea, early satiety, gastro-oesophageal reflux, and mechanical low-back pain. Other complications caused by mass effect include hepatic venous outflow obstruction, compression of the inferior vena cava, portal-vein compression, or bile-duct compression presenting as obstructive jaundice.¹⁴⁹

Symptomatic cyst complications include cyst haemorrhage, infection, and occasional torsion or rupture. The typical presentation of cyst infection is with localised pain, fever, leucocytosis, raised sedimentation rate, and often increased alkaline phosphatase.¹⁵⁰ It is usually mono-microbial and caused by enterobacteriaceae. MRI is very sensitive for the identification of a complicated hepatic

cyst. On CT, fluid-debris concentrations within cysts, cyst wall thickening, intracystic gas bubbles, and heterogeneous or increased density have been associated with infection. Radionuclide imaging and, more recently, 18-F-fluorodeoxyglucose positron emission tomography scanning have been used for diagnosis.¹⁵¹

Mild dilatation of the common bile duct has been seen in 40% of patients studied by CT and can occasionally be associated with episodes of cholangitis.¹⁵² Rare associations of polycystic liver disease include congenital hepatic fibrosis,¹⁵³ adenomas of the ampulla of Vater,¹⁵⁴ and cholangiocarcinoma.¹⁵⁵

Cysts in other organs

Cysts of the seminal vesicles, pancreas, and arachnoid membrane are present in 40% (of men), 5%, and 8% of patients, respectively.^{156–161} Seminal vesicle cysts rarely result in infertility.¹⁶² Defective sperm motility is another cause of male infertility in autosomal dominant polycystic kidney disease.¹⁶³ Pancreatic cysts are almost always asymptomatic, with very rare instances of recurrent pancreatitis and possibly chance associations of intraductal papillary mucinous tumour or carcinoma.^{164–166} Arachnoid membrane cysts are asymptomatic, but can increase the risk of subdural haematomas.^{158,167} Spinal meningeal diverticula can occur with increased frequency and rarely present with intracranial hypotension due to cerebrospinal fluid leak.¹⁶⁸ Ovarian cysts are not associated with autosomal dominant polycystic kidney disease.^{169,170}

Vascular manifestations

These include intracranial aneurysms and dolichoectasias, thoracic aortic and cervicocephalic artery dissections, and coronary artery aneurysms. They are caused by alterations in the vasculature directly linked to mutations in *PKD1* or *PKD2*. Polycystin-1 and polycystin-2 are expressed in vascular smooth muscle cells.^{105–107} *Pkd2*^{-/-} vascular smooth muscle cells exhibit increased rates of proliferation and apoptosis and *Pkd2*^{-/-} mice have an increased susceptibility to vascular injury and premature death when induced to develop hypertension.^{20,64}

Intracranial aneurysms occur in around 6% of patients with a negative family history of aneurysms and 16% of those with a positive history.¹⁷¹ They are most often asymptomatic. Focal findings such as cranial nerve palsy or seizure result from compression of local structures. The risk of rupture depends on many factors, described later. Rupture carries a 35–55% risk of combined severe morbidity and mortality.¹⁷² Mean age at rupture is lower than in the general population (39 years vs 51 years). Most patients have normal renal function and up to 29% have normal blood pressure at the time of rupture.

Cardiac manifestations

Mitral valve prolapse is the most common valvular abnormality found in up to 25% of patients on echocardiography.^{173,174} Aortic insufficiency can occur in

association with dilatation of the aortic root.¹⁷⁵ Although these lesions can progress with time, they rarely need valve replacement. Screening echocardiography is not indicated unless a murmur is detected on examination.

Diverticular disease

Colonic diverticulosis and diverticulitis are more common in ESRD patients with autosomal dominant polycystic kidney disease than in those with other renal diseases.^{176–178} Whether this heightened risk extends to patients before ESRD is uncertain.¹⁷⁹ There have been reports of extracolonic diverticular disease.¹⁸⁰ The disease might become clinically significant in a few patients. Subtle alterations in polycystin function can enhance the smooth-muscle dysfunction from ageing thought to underlie the development of diverticula.

Treatment

Current treatment is directed towards reducing morbidity and mortality due to the complications of the disease.

Hypertension

There is no proven antihypertensive drug of choice. ACE inhibitors or angiotensin receptor blockers increase renal blood flow, have a low side-effect profile, and can have renoprotective properties beyond blood-pressure control.^{93–95} Some studies have shown better preservation of renal function or reduction in proteinuria and left ventricular hypertrophy with ACE inhibitors or angiotensin receptor blockers compared with diuretics or calcium channel blockers.^{117,181–183} whereas others have been unable to prove an increased benefit with these drugs.¹⁸⁴ A meta-analysis of 142 patients with autosomal dominant polycystic kidney disease in eight randomised clinical trials showed that ACE inhibitors were more effective than were other antihypertensive agents in lowering urine protein excretion and slowing kidney-disease progression in patients with higher levels of proteinuria, but overall kidney-disease progression was not significantly different (29% in the ACE inhibitor group vs 41% in the control group).¹⁸⁵ Most studies have been limited by inadequate power, short follow-ups, wide ranges of renal function, and doses with inadequate pharmacological effects.

Equally uncertain is the optimum blood-pressure target. In the Modification of Diet in Renal Disease (MDRD) study, patients with autosomal dominant polycystic kidney disease with a baseline GFR of between 13 and 24 mL/min/1.73 m² assigned to a low mean arterial blood-pressure target (<92 mm Hg) had faster decline in GFR than those assigned to a standard blood-pressure goal (<107 mm Hg), possibly because of the inability to autoregulate renal blood flow.¹²⁶ The rate of decline in participants with a baseline GFR between 25 and 55 mL/min/1.73 m² was not affected by the blood-pressure target over a mean intervention period of 2.2 years. However, an extended follow-up of these patients showed a delayed onset of kidney failure and a reduced composite

outcome of kidney failure and all-cause mortality in the low blood-pressure group (51% of them taking ACE inhibitors) compared with those in the usual blood-pressure group (32% of them taking ACE inhibitors).¹⁸⁶ The size of this beneficial effect was similar to that observed in patients with other renal diseases.

Until more information becomes available, it seems reasonable to control the blood pressure to less than 130/80 mm Hg with a regimen that includes ACE inhibitors or angiotensin receptor blockers. An ongoing study (HALT-PKD) is designed to determine whether combined treatment with an ACE inhibitor and an angiotensin receptor blocker is better than an ACE inhibitor alone in delaying the progression of cystic disease in patients with stage 1 or 2 chronic kidney disease or in slowing down the decline of renal function in patients with stage 3 disease. HALT-PKD will also determine whether a low blood-pressure target (<110/75 mm Hg) is better than a standard blood-pressure target (<130/80 mm Hg) in the group of patients with preserved function.

Children at risk of autosomal dominant polycystic kidney disease should be monitored for early disease presentations that need treatment. Among these, hypertension is under-recognised. The presence of palpable kidneys or polyuria should prompt a careful assessment of blood pressure.⁹⁷ Children with hypertension have higher left ventricular mass and faster growth of the kidneys than those without.¹³³ An ongoing clinical trial of antihypertensive treatment (starting with an ACE inhibitor) seeks to determine whether tight blood-pressure control (>50% of measurements at or below the 50th percentile) is better than standard blood-pressure control (at or below the 90th percentile) in this population.¹⁸⁷

Pain

Causes of pain that might need intervention, such as infection, stones, or tumours, should be excluded. Long-term administration of nephrotoxic drugs should be avoided. Narcotic analgesics should be reserved for acute episodes. Psychological assessment and an understanding and supportive attitude on the part of the physician are essential to minimise the risk of narcotic and analgesic dependence in patients with chronic pain. Reassurance, lifestyle modification, avoidance of aggravating activities, tricyclic antidepressants, and pain clinic interventions such as splanchnic nerve blockade with local anaesthesia or steroids might be helpful.^{118,119}

When conservative measures fail, surgical interventions can be considered. Aspiration of large cysts under ultrasound or CT guidance is a simple procedure and might help to identify the cause of the pain. Sclerosing drugs might be used to prevent the reaccumulation of fluid. When multiple cysts contribute to pain, laparoscopic or surgical cyst fenestration through lumbotomy or flank incisions might be of benefit.¹⁸⁸ Laparoscopy is as effective as open surgical fenestration for patients with limited disease and has a shorter, less complicated recovery

period.^{189,190} Laparoscopic or thoracoscopic renal denervation can be considered in rare cases, especially in polycystic kidneys without large cysts.^{191,192} Surgical interventions do not accelerate the decline in renal function, as once thought, but do not preserve declining renal function either. Laparoscopic or retroperitoneoscopic nephrectomy is indicated for symptomatic patients with ESRD.¹⁹³

Cyst haemorrhage

Cyst haemorrhages are usually self-limiting and respond to conservative management with bed rest, analgesics, and hydration. When there is a subcapsular or retroperitoneal haematoma causing significant decrease in haematocrit and haemodynamic instability, hospitalisation, transfusion, and investigation by CT or angiography become necessary. Segmental arterial embolisation or surgery might be needed in some cases.

Cyst infection

Cyst infections are often difficult to treat.¹²⁴ Treatment failure can occur because of poor antibiotic penetration into the cysts. Lipophilic agents penetrate the cysts consistently. If fever persists after 1–2 weeks of appropriate antimicrobial treatment, percutaneous or surgical drainage of infected cysts or, in the case of end-stage polycystic kidneys, nephrectomy should be undertaken. If fever recurs after stopping antibiotics, complicating features such as obstruction, perinephric abscess, or stone should be excluded. If none is identified, several months of antibiotic treatment might be needed to eradicate the infection.

Nephrolithiasis

Generous water intake should be recommended as a prophylactic measure. Potassium citrate is indicated for three causes of stones associated with autosomal dominant polycystic kidney disease, uric acid lithiasis, hypocitraturic calcium oxalate nephrolithiasis, and distal acidification defects. Extracorporeal shockwave lithotripsy and percutaneous nephrostolithotomy have been undertaken successfully without undue complications.

End-stage renal disease

Patients with autosomal dominant polycystic kidney disease do better on dialysis than do patients with other causes of ESRD. This finding could be due to higher concentrations of erythropoietin and haemoglobin or to lower comorbidity.¹⁹⁴ Peritoneal dialysis can be undertaken when the kidneys are not too large, although there is an increased risk of hernias.

Transplantation is the treatment of choice for ESRD in autosomal dominant polycystic kidney disease. There is no difference in patient or graft survival between patients with this disease and other ESRD populations. The number of living donor transplants for autosomal dominant polycystic kidney disease in the USA has increased from 12% in 1990 to 30% in 1999. Complications after transplantation are no

greater than in the general population. Complications directly related to the disease are rare. Pretransplant nephrectomy is reserved for patients with a history of infected cysts or frequent bleeding.¹⁹⁵ Hand-assisted laparoscopic nephrectomy is increasingly being used.

Polycystic liver disease

Most cases of polycystic liver disease do not need treatment. Patients with severe disease should avoid oestrogens and compounds that promote cAMP accumulation (eg, caffeine). Rarely, symptomatic disease requires interventions to reduce cyst volume and hepatic size. The choice of procedure (percutaneous cyst aspiration with or without sclerosis, laparoscopic cyst fenestration, combined liver resection and cyst fenestration, and liver transplantation) is dictated by the anatomy and distribution of the cysts.^{196–200}

Combined percutaneous cyst drainage and antibiotic treatment provide the best treatment results for hepatic cyst infections.¹⁵⁰ Long-term oral antibiotic suppression or prophylaxis is indicated for relapsing or recurrent cases. Fluoroquinolones and trimethoprim-sulfamethoxazole are effective against the typical infecting organisms and have good penetration into the biliary tree and cysts.

Intracranial aneurysm

Widespread presymptomatic screening is not indicated because it yields mostly small aneurysms with a low risk of rupture. Indications for screening in patients with good life expectancy include family history of aneurysm or subarachnoid haemorrhage, previous aneurysm rupture, preparation for major elective surgery, high-risk occupations (eg, airline pilots), and patient anxiety despite adequate information.¹⁷⁰ Magnetic resonance angiography does not require intravenous contrast material. CT angiography is a satisfactory alternative when there is no contraindication to intravenous contrast.

When an asymptomatic aneurysm is found, a recommendation for whether to intervene depends on its size, site, and morphology, history of subarachnoid haemorrhage from another aneurysm, the patient's age and general health, and whether the aneurysm is coilable or clippable. The prospective arm of ISUIA (International Study of Unruptured Intracranial Aneurysms) has provided invaluable information to assist in decisionmaking.²⁰¹ The 5 year cumulative rupture rates for patients without a previous history of subarachnoid haemorrhage with aneurysms located in the internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7–12 mm, 13–24 mm, and 25 mm or greater, respectively, compared with rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories affecting the posterior circulation and posterior communicating artery. Among unruptured non-cavernous segment aneurysms less than 7 mm in diameter, the rupture risks were higher among those who

had a previous subarachnoid haemorrhage from another aneurysm than for those who did not. These risks need to be balanced with those associated with surgical or endovascular surgery also reported by ISUIA. The 1 year mortality and combined morbidity (Rankin score 3–5 or impaired cognitive status) and mortality rates for surgical or endovascular repair were 2.7% and 12.6%, respectively, for open surgery and 3.4% and 9.8%, respectively, for endovascular repair.

The risk of new aneurysms or enlargement of an existing one in patients with autosomal dominant polycystic kidney disease is very low in those with small (<7 mm) aneurysms detected by presymptomatic screening and moderate in those with a previous rupture from a different site.^{202,203} On the basis of these and the ISUIA data, conservative management is usually recommended for patients with small (<7 mm) aneurysms identified with presymptomatic screening, particularly in the anterior circulation. Semi-annual or annual repeat imaging studies are appropriate initially, but reassessment at less frequent intervals might be sufficient once the stability of the aneurysm has been documented. Elimination of tobacco use and aggressive treatment of hypertension and hyperlipidaemia is recommended.

The risk of developing a new aneurysm after an initial negative study is small at about 3% at 10 years in patients with a family history of intracranial aneurysms.²⁰⁴ Therefore, rescreening of patients with a family history of intracranial aneurysms after 5–10 years seems reasonable.

New treatments

A better understanding of the pathophysiology and the availability of animal models has enabled the development of preclinical trials and the identification of promising candidate drugs for clinical trials.

The effect of vasopressin, via V2 receptors, on cAMP concentrations in the collecting duct, the major site of cyst development in autosomal dominant polycystic kidney disease, and the role of cAMP in cystogenesis provided the rationale for preclinical trials of vasopressin V2 receptor (VPV2R) antagonists. One of these drugs, OPC-31260, substantially reduced concentrations of cAMP and inhibited cyst development in models of autosomal recessive and autosomal dominant polycystic kidney disease and nephronophthisis.^{61,62,85} An antagonist with high potency and selectivity for the human VPV2R (tolvaptan) has also been shown to be an effective treatment in the rat model of autosomal recessive polycystic kidney disease²⁰⁵ and the *Pkd2* mouse model of autosomal dominant polycystic kidney disease (unpublished). These drugs have no effect on liver cysts, consistent with the absence of VPV2R in the liver. High water intake by itself also exerts a protective effect on the development of polycystic kidney disease in the rat model, probably owing to suppression of vasopressin.⁸⁶ Phase II clinical trials with tolvaptan have been completed and a phase III clinical trial is scheduled to start later this year.

Somatostatin acting on SST2 receptors inhibits cAMP accumulation not only in the kidney but also in the liver. Octreotide, a synthetic metabolically stable somatostatin analogue, halts the expansion of hepatic cysts from a rat model of polycystic kidney disease in vitro and in vivo. Similar effects were seen in the kidneys of the rat model.²⁰⁶ These observations are consistent with the inhibition of renal growth in a pilot study of long-acting octreotide for human autosomal dominant polycystic kidney disease²⁰⁷ and provide support for further clinical trials for polycystic kidney disease and polycystic liver disease.

Patients with the contiguous *PKD1-TSC2* gene syndrome have a more severe form of polycystic kidney disease than those with autosomal dominant polycystic kidney disease alone.²⁰⁸ This observation suggests a convergence of signalling pathways downstream from polycystin-1 and tuberous sclerosis protein tuberin. Activation of mTOR in polycystic kidneys and an interaction between polycystin-1 and the tuberin have been reported.²⁰⁹ Furthermore, studies in three rodent models of polycystic kidney disease have shown that sirolimus significantly retards cyst expansion and protects renal function.^{209–211} Phase II clinical trials of sirolimus and everolimus, two mTOR inhibitors, are being implemented.²¹²

Other drugs shown to be effective in preclinical trials and of potential value for the treatment of human polycystic kidney disease include inhibitors of Erb-B1 (epidermal growth factor receptor),²¹³ Erb-B2 tyrosine kinase,²¹⁴ Src kinase,⁶⁸ MEK,²¹⁵ and CDK.⁶⁹ These drugs, which have been developed for the treatment of neoplastic diseases, may also be considered for the treatment of polycystic kidney disease.

In planning clinical trials for autosomal dominant polycystic kidney disease, the use of renal function as the primary outcome becomes an issue. Decades of normal renal function, despite progressive enlargement and cystic transformation of the kidneys, characterise the natural history of the disease. By the time the GFR starts declining, the kidneys are greatly enlarged, distorted, and unlikely to benefit from treatment. On the other hand, early interventional trials would require unrealistic periods of follow-up if renal function was to be used as the primary outcome. The results of CRISP⁸² have shown that the rate of renal growth is a good predictor of functional decline and justify the use of kidney volume as a surrogate marker of disease progression in clinical trials for the disease.

Conflict of interest statement

VET has received a grant from Otsuka and is participating in an Otsuka sponsored clinical trial. PCH is named on a PKD1 patent held by the Medical Research Council (UK), but any future income will be donated to the PKD Foundation. YP has received a fee for speaking from Amgen.

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