Autosomal Dominant Polycystic Kidney Disease
Markedly enlarged polycystic kidneys from a patient with ADPKD in comparison to a normal kidney in the middle.
ADPKD is a multisystem disorder characterized by multiple, bilateral renal cysts associated with cysts in other organs, such as liver, pancreas, and arachnoid membranes.

It is a genetic disorder mediated primarily by mutations in two different genes and is expressed in an autosomal dominant pattern, with variable expression.

Approximately 5% of patients who initiate dialysis annually in the United States.
PKD Genetics

**Incidence**

- **Autosomal Dominant** 1:500-1,000 live births
- **Autosomal Recessive** 1:6,000-40,000 live births
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADPKD1</td>
<td>Polycystin 1</td>
</tr>
<tr>
<td>ADPKD2</td>
<td>Polycystin 2</td>
</tr>
<tr>
<td>ARPKD</td>
<td>Fibrocystin/polyductin</td>
</tr>
</tbody>
</table>
ADPKD - Molecular Pathogenesis

- Incidence \(\sim 1:1,000\)
  - \(\text{PKD1} - 85\%\)
  - \(\text{PKD2} - 10-15\%\)

- PKD1-related disease more severe than PKD2-related disease
Family History of Severity of Renal Disease Predicts Mutated Gene in ADPKD

Median Age of ESRD

PKD1 ~ 53 years

PKD2 ~ 73 years

- Presence of at least one affected family member who developed ESRD ≤ 55 years was highly predictive of PKD1 mutation (PPV 100%, sensitivity 72%)

- If family member developed ESRD at age ≥ 70 years, then highly predictive of PKD 2 mutations (PPV 100%, Sensitivity 74%)

Barau et al JASN20: 1833, 2009
Etiology and Pathogenesis

• The polycystic kidney disease (PKD) proteins now known as **polycystin 1 (PC1)** and **polycystin 2 (PC2)** play a critical role in the normal function of the **primary cilium** that is essential to maintaining the differentiated phenotype of tubular epithelium.

• **Disordered function of polycystins is the basis for cyst formation** in PKD by permitting a less differentiated tubular epithelial phenotype.
Cilia in ADPKD

**FIGURE 16.6** Polycystin (PC) signaling effector pathways. The PC-1/PC-2 receptor channel sensory complex on apical cilia on the renal tubular epithelium is activated by flow and potential ligands carried by the flow (exosome-like vesicles [ELVs]). This is thought to result in a rise in local and cellular calcium, which mediates signals to a number of effector pathways. Pathways or components shown in blue are activated by normal polycystin signaling, whereas those shown in red are inhibited by intact polycystin signals. A loss of PCs results in increased cyclic adenosine monophosphate (cAMP) production, which may increase apical secretion and the proliferation in cyst cells. The loss of PCs also increases the progression of the cell cycle, and may activate mammalian target of rapamycin (mTOR) signaling and may favor β-catenin-dependent Wnt signaling. STAT1, signal transducers and activators of transcription 1; CFTR, cystic fibrosis transmembrane conductance regulator; MAPK/ERK, mitogen-activated protein kinase/extracellular regulated kinase. (See Color Plate.)
Cystogenesis

• Fluid Secretion into Cysts

• Increased cAMP promotes cyst growth and overall enlargement

• Increased transepithelial secretion of chloride through apical CFTR channels
PATHOGENESIS
Polycystic kidney

Polycystic nephron

Renal tubule

Non-genetic factors
Circulating agents (vasopressin, cAMP, EGF and Src activators, ouabain)

Transepithelial fluid secretion

Pathophysiological mechanisms

Cell proliferation
Alteration in cell planar polarity
Remodeling of the ECM
Cell cilia malfunction

Genetic factors
Germ-line mutation of Pkd1 and Pkd2
Second somatic mutation
Diagnosis

- Imaging tests the gold standard

- At present, asymptomatic screen not recommended

- Ultrasound: false negative rate 16-18% before age 30

- CT, MR: probably more sensitive
## 16.2 Diagnostic Criteria for Autosomal Dominant Polycystic Kidney Disease

<table>
<thead>
<tr>
<th>Age</th>
<th>PKD1</th>
<th>PKD2</th>
<th>Unknown ADPKD Gene Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39 years</td>
<td>$\geq 3$ cysts$^a$</td>
<td>$\geq 2$ cysts in each kidney</td>
<td>$\geq 3$ cysts$^a$</td>
</tr>
<tr>
<td></td>
<td>PPV = 100%</td>
<td>PPV = 100%</td>
<td>PPV = 100%</td>
</tr>
<tr>
<td></td>
<td>SEN = 96.6%</td>
<td>SEN = 94.9%</td>
<td>SEN = 95.5%</td>
</tr>
<tr>
<td>40–59 years</td>
<td>$\geq 2$ cysts in each kidney</td>
<td>PPV = 100%</td>
<td>PPV = 100%</td>
</tr>
<tr>
<td></td>
<td>PPV = 100%</td>
<td>PPV = 100%</td>
<td>PPV = 100%</td>
</tr>
<tr>
<td></td>
<td>SEN = 92.6%</td>
<td>SEN = 88.8%</td>
<td>SEN = 90%</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39 years</td>
<td>$\leq 1$ cyst</td>
<td>$\leq 1$ cyst</td>
<td>$\leq 1$ cyst</td>
</tr>
<tr>
<td></td>
<td>NPV = 100%</td>
<td>NPV = 96.8%</td>
<td>NPV = 98.3%</td>
</tr>
<tr>
<td></td>
<td>SPEC = 96%</td>
<td>SPEC = 93.8%</td>
<td>SPEC = 94.8%</td>
</tr>
<tr>
<td>40–59 years</td>
<td>$\leq 1$ cyst</td>
<td>$\leq 1$ cyst</td>
<td>$\leq 1$ cyst</td>
</tr>
<tr>
<td></td>
<td>NPV = 100%</td>
<td>NPV = 100%</td>
<td>NPV = 100%</td>
</tr>
<tr>
<td></td>
<td>SPEC = 93.9%</td>
<td>SPEC = 93.7%</td>
<td>SPEC = 94.8%</td>
</tr>
</tbody>
</table>

$^a$Unilateral or bilateral.
All values presented are mean estimates.
Genetic Testing

- DNA screen of polycystin 1 and polycystin 2 available

- Up to 90% detection rate – better with affected family members

- Expensive: $2,000-2,500

- Non-important mutation rate unknown
Differential Diagnosis

• Syndromes Mimicking ADPKD
  – Von Hippel-Lindau
  – Tuberous Sclerosis
• ARPKD
• Simple Renal Cysts
• Acquired Cystic Disease of Renal Failure
• Medullary Cystic Disease/Nephronophthisis
### Table 1. Other Renal Cystic Disorders.*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cysts</th>
<th>Renal Cyst Distribution</th>
<th>Age at Detection</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple cysts</td>
<td>Few</td>
<td>Diffuse</td>
<td>All ages</td>
<td>Benign</td>
</tr>
<tr>
<td>Acquired cystic disease</td>
<td>Few to many</td>
<td>Diffuse</td>
<td>Adulthood</td>
<td>Cyst development preceded by renal failure</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Few to many</td>
<td>Diffuse</td>
<td>All ages</td>
<td>Renal angiomyolipomas; may be associated with dermatologic findings (adenoma sebaceum, café au lait patches), periungual fibroma, retinal hamartomas, or cardiac rhabdomyoma</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney disease</td>
<td>Many</td>
<td>Radial pattern</td>
<td>Often present at birth; childhood in some cases</td>
<td>Huge kidneys; associated with congenital hepatic fibrosis</td>
</tr>
<tr>
<td>Hereditary cystic diseases with interstitial nephritis</td>
<td>Few to many</td>
<td>Medullary</td>
<td>Childhood; adulthood in a few cases</td>
<td>Early renal failure; may be associated with retinitis pigmentosa, truncal cerebellar ataxia, or gout</td>
</tr>
</tbody>
</table>

* Conditions are listed in order of decreasing prevalence. Information is from Torres and Grantham.¹
Clinical Manifestations

- Renal and extrarenal manifestations of ADPKD have been described that cause significant complications.
Renal Complications

1. Hypertension 60-100%
2. Gross hematuria 50%
3. Infection common
4. Nephrolithiasis 20-25%
5. Renal failure 50% by age 60 (PKD1)
Relationship between HTN, GFR loss and TKV

- Across all age ranges **HTN** is noted when TKV is \( \sim 1000 \text{ mL} \) (~600 mL/cm height)

- **GFR** decrease not detected until total kidney volume exceeds **1500 ml**

- Current US techniques too variable to be used as a marker for yearly progression of ADPKD

*Kidney International, 64: 1035–1045, 2003*
*Kidney International, 64: 2214–2221, 2003*
Loss of kidney function in ADPKD

**Figure 16.8** A proposed relationship between renal cyst burden, age, and renal function in autosomal dominant polycystic kidney disease (ADPKD). Coronal magnetic resonance imaging (MRI) of four ADPKD individuals age 9, 20, 21, and 40 with normal renal function are overlaid on a plot of glomerular filtration rate (GFR) as a function of age in ADPKD patients. Although hypertension, pain, hematuria, urinary tract infections (UTIs), and nephrolithiasis occur throughout the course of ADPKD, renal function remains largely intact until total kidney volume reaches a size where renal reserve no longer can compensate. Thereafter, renal function inexorably declines to end-stage renal disease. (Adapted with permission from Torres V, Scheinman S. Polycystic kidney diseases. *Nephrol Pract*. Jan 2004;3(1):22.)
Mechanisms of Hypertension in ADPKD

Normal kidney

ADPKD kidney
Pathogenetic role of RAAS in ADPKD

Cyst compression of renal vasculature

↗Renin

↗Angiotensin II

Increased
growth factors

Angiogenesis

↗Endothelin

↗Sympathetic
activity

Oxidant-
mediated endothelial
damage

↗Aldosterone

Transforming
growth factor
beta

↗Cyst proliferation
and expansion

↗Systemic vascular resistance

↗Sodium
retention

↗Renal
fibrosis

Hypertension and
renal disease

Schrier JASN 20:1888-1893, 2009
Hypertension in PKD

- Control most important to prevent progression
- ACE inhibitors, ARBs theoretically better
- Blood pressure goal not established (should be to less than 130/80 mmHg)
- BP goal of less than 120/80 mmHg may provide cardiovascular benefit among ADPKD patients with left ventricular hypertrophy
Diet in PKD

- Avoid caffeine
- No specific diet known
- DASH diet reasonable
Nephrolithiasis in ADPKD

- ~20-36% of patients
- **Uric acid (UA)** (~50%); **Ca Ox** (~47%)
- Predisposing factors: hypocitraturia, hyperoxaluria, hypercalciuria, urinary stasis from expanding cysts, **Low urine pH**
- **Rx:** K-citrate, Alkalinization of urine, hydration
- Lithotripsy can be performed safely, but residual fragments in ~50% of patients
Hematuria in ADPKD

• Cyst hemorrhage occurs in ~60% of individuals
• Associate with rapid cyst expansion, increased physical activity, and cyst wall calcifications
• Associated with increased kidney size and a poorer renal prognosis
• Conservative management with hydration, bed rest, and appropriate use of analgesics
• Rarely, massive bleeding may require transfusion, kidney embolization or nephrectomy
Kidney Infection in ADPKD

- 30 to 50% (more common in women)
- Cyst infections ~ 0.01 episode/patient/year (10% of causes that led to hospitalization)
- Fever and Flank pain are the presenting symptoms
- Urine culture may be negative in cyst infection, as cysts frequently don’t communicate with the collecting system. (E coli ~ 75% of cases)
- (+) urine culture ~39%, (+) blood culture ~24% in renal cysts infection
Infected cysts in PKD

- Localization of infected cysts is difficult
  - Labeled WBC or gallium scan (positive in ~50% of cases)
  - CT&MRI with contrast (good for R/O renal or perinephric abscesses)
  - PET scan

- Ultrasound, CT scan, MRI, and PET scan yielded positive results in 6, 18, 40, and 100%, respectively for infected cysts

Antibiotics in PKD

- Some drugs do not penetrate cysts well
- Fluoroquinolones, Tmp-Sulfa, chloramphenicol best for cyst penetration
- Percutaneous or operative drainage is rarely needed; only refractory infection
- Complicated upper tract: cyst penetrating, antibiotics 3-4 weeks
Table 5. Published data regarding intracyst antibiotic diffusion in patients with ADPKD

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Cyst Location</th>
<th>Antibiotic</th>
<th>Intracystic Antibiotic Diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telenti et al. (7)</td>
<td>3</td>
<td>Liver</td>
<td>Ciprofloxacin</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 2.3 to 4.4</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>Chloramphenicol</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 1.1</td>
</tr>
<tr>
<td>Bennett et al. (17)</td>
<td>10</td>
<td>Kidney</td>
<td>Amoxicillin</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aminoside</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clindamycin</td>
<td>Good</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Metronidazole</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bactrim</td>
<td>Good</td>
</tr>
<tr>
<td>Elzinga et al. (18)</td>
<td>7</td>
<td>Kidney</td>
<td>Ciprofloxacin (oral)</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 2.5</td>
</tr>
<tr>
<td>Hiyama et al. (12)</td>
<td>1</td>
<td>Kidney</td>
<td>Ampicillin</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum &lt;0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levofoxacin</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 0.96</td>
</tr>
<tr>
<td>Elzinga et al. (19)</td>
<td>8</td>
<td>Kidney</td>
<td>Trimethoprim</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum &gt;8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sulfamethoxazole</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 0.1 to 0.7</td>
</tr>
<tr>
<td>Schwab et al. (20)</td>
<td>1</td>
<td>Kidney</td>
<td>Trimethoprim</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 1.6 to 23.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sulfamethoxazole</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 0.07 to 0.70</td>
</tr>
<tr>
<td>Schwab et al. (21)</td>
<td>1</td>
<td>Kidney</td>
<td>Clindamycin</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 2.4 to 8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gentamycinc</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentration ratio cyst/serum 0.18 to 0.34</td>
</tr>
</tbody>
</table>

Principal Extrarenal Manifestations

- **Hepatic and pancreatic cysts**
  - asymptomatic in many patients, but can expand and cause pain and infection
- **Cardiac valvular abnormalities**
  - Mitral valve prolapse, tricuspid and aortic regurgitation
- **Intracranial aneurysms**
  - Found in approximately 5% of patients with no family history and about 22% of patients with family history of ICA or SAH
- **Seminal vesicle cysts**
  - Found in ~39-60% of men; undefined risk of infertility
Liver/GI Complications

1. Liver cysts (94% > 35)
   asymptomatic up to 80%
   symptomatic uncommon (W:M 10:1)
2. Pancreatic cysts ~10%
3. Intestinal diverticuli ~80% pts with ESRD
4. Hernias ~10%
Liver Cysts: Sx and Infection

- With marked hepatomegaly: Heaviness, dull ache, Mechanical low back pain, Early satiety
- If fever persists 1-2 wks after antibiotics in infected cysts, drainage frequently needed
- Hepatic cyst infection more serious than renal cyst infection. Do not delay drainage esp >5cm
- ↑ serum ALK-P, Bil-T, ↓ total cholesterol and triglyceride levels

Kanaan et al AJKD March, 2010
Vascular manifestations of ADPKD.

A, Gross specimen demonstrating bilateral aneurysms of the middle cerebral arteries.

   90% of aneurysms in anterior circulation
   10% of aneurysms in posterior circulation (greater risk of rupture)

B, Gross specimen demonstrating a thoracic aortic dissection extending into the abdominal aorta in a patient with ADPKD.
Cerebral Aneurysm in ADPKD

- 6.6-fold increased likelihood
- No family history – 6% prevalence
- Family history – 21% prevalence
- Clinical Symptoms (Ruptured) – pain, stiff neck, coma; >50% mortality
- The mean age of rupture of intracranial aneurysms is lower in individuals with ADPKD than in the general population (39 years vs 51 years)
## Risk of ICA Rupture in ADPKD

In the absence of a history of rupture from a different site, the risk for rupture is:

<table>
<thead>
<tr>
<th>%Yr</th>
<th>Aneurysm Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>&lt;10 mm</td>
</tr>
<tr>
<td>1.0</td>
<td>10-24 mm</td>
</tr>
<tr>
<td>6.0</td>
<td>&gt;24 mm</td>
</tr>
</tbody>
</table>

- 0.05% per year <10mm. No personal or family hx of SAH
- 0.5% per year<10 mm. With personal or family hx of SAH

Betz KI 63:2003
Gibbs KI 64:2004
Risk Factors for ICA Rupture

1. Most aneurysms have a very low risk of rupture and occurs without a family history
2. With 2 PKD relatives with SAH the RR= 2.15
3. F>M and ICA>8mm
4. Pack years of smoking
5. HTN > 10 years

Torres 2009
Recommendations for ICA Screening

1. Age 20- to 50-year-olds
2. Family Hx of ICA or SAH
3. Personal Hx of SAH
4. Prior to major elective surgery (transplant)
5. High risk occupation (Airline Pilots)
6. Need for reassurance?

Torres 2009
Risks of Intervention

- Mortality: 0.6-3.5%
- Morbidity: 4.1-25.4%
F/U of ICA in ADPKD

• <7 mm    Observation
• 7-12 mm  Risk assessment
• >12 mm   Intervene

• Follow-up with CTA or MRA annually for two to three years, and every two to five years thereafter if the aneurysm is clinically and radiographically stable.
• It is not unreasonable to reimage newly detected small aneurysms at six months.
Treatment

• Novel Treatment
  – V2 receptor antagonists (Tolvaptan)
  – mTOR inhibitors (Rapamycin)
  – Somatostatin
  – EGF receptor antagonists

• Transplantation
  – The treatment of choice for ESRD in ADPKD.
Water in Treatment in PKD

Tubule cell proliferation – Transepithelial fluid secretion

\[ \text{cAMP stimulates growth} \]

- Enlarging Renal cysts
- V2 receptor
- AVP (ADH)

Renal dysfunction

Blocking action of AVP dramatically ameliorates the disease process

Torres, Bankir, Grantham  CJASN: 4: 1140-1150, 2009
Thanks