Fellow Seminar

Autosomal Dominant Polycystic Kidney Disease

F2 吳逸文醫師, 25/08/2004
Familial Nephronophthisis

ARPKD

ADPKD

Polycystic Kidney Disease

Nephrocytin

Fibrocytin

Acidic

SH₃

Polycystin-1

Polycystin-2

ADPKD

ARPKD

DKFZ

PKA or PKC
PKD1 vs PKD2 genes

**PKD1 gene 16p13.3**
- 46 exons
- 4302 amino acids
- **Distribution:**
  - kidney
  - (distal nephron and collecting duct)
  - brain
  - heart
  - bone
  - muscle
- **Mutations:** (85%)
  - splice site, in-frame, out-frame deletion or insertion
  - non-sense mutation

**PKD2 gene 4q 21-23**
(1996):
- 15 exons
- 968 amino acids
- **Distribution:**
  - Kidney
  - (except thin limbs and glomeruli)
  - Heart
  - Ovary
  - Testis
  - Vascular (SM)
  - Small intestine
- **Mutation:** (15%)
  - frameshift
  - splicing
  - nonsense mutation

Unknown **PKD3 gene?**
short arm of Chro 7
ADPKD is a focal disease?  
“Two-hit hypothesis”

- germline mutated PKD1 (or PKD2) allele
- wild-type gene

**Animal model:**
**Heterozygous Pkd2^ws25/-** mice:
- renal cyst
- immunostaining of polycystin in renal tubules but not in cyst

Igarashi, JASN, 13, 2002
Mutation and disease severity

- Poor genotype/phenotype correlation, except:

  @ PKD2 gene mutation:
  Milder disease severity
  Presentation later in the life
  Longer renal survival
  Fewer complication

  @ PKD1 gene mutation:
  in 5’ end was associated with earlier onset of disease
  than mutation in 3’ end
Our experience: Characteristics of 20 patients with ADPKD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men/women)</td>
<td>11/9</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>55.2 ±15.7</td>
</tr>
<tr>
<td>Patients with ESRD</td>
<td>11/20 (55%)</td>
</tr>
<tr>
<td>Mean age of ESRD (years)</td>
<td>52.6±11.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Ruptured Intracranial aneurysm</td>
<td>1/20 (5%)</td>
</tr>
<tr>
<td>Mean Cr in patients without ESRD (mg/dl)</td>
<td>1.6 ± 0.8</td>
</tr>
</tbody>
</table>

Note: Values expressed as mean ± SD

Chang MY, CGMH, poster of TSN, 2003
## Mutations in the PKD2 gene in 3 patients (15%)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>Location</th>
<th>Nucleotide Change</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nonsense: Y227X</td>
<td>Exon 2</td>
<td>C681A</td>
<td>ESRD at age of 50</td>
</tr>
<tr>
<td>2</td>
<td>Frameshift: 712→715X</td>
<td>Exon 11</td>
<td>2136-2137delG</td>
<td>Cr 1.5 at age of 70; Cardiac valve abnormality; Cardiac conduction defect</td>
</tr>
<tr>
<td>3</td>
<td>Nonsense: R803X</td>
<td>Exon 13</td>
<td>C2407T</td>
<td>ESRD at age of 52; Urolithiasis</td>
</tr>
</tbody>
</table>

Chang MY, CGMH, poster of TSN, 2003
Figure 1: Sequence data showing three PKD2 gene mutations:
(A) Nonsense mutation Y227X; C681A; (B) Frameshift mutation 712-715 X; 2136-2137delG
(C) Nonsense mutation R803X; C2407T.
Interfamilial and intrafamilial heterogeneity...modifier gene?

Germline mutations

Genotype

DNA instability

Modifier genes:
Angiotensin I converting enzyme gene deletion polymorphism
ENOS (NOS3) gene polymorphism

Phenotype

Devuyst, NDT, 18, 2003
@ Genetics
 @ Cell biology and pathogenesis
 @ Clinical picture
 @ Complication
 @ Treatment prospects
 @ Outcome
 @ Screening & genetic counseling
Role of polycystins:

1. Mechanoreceptor
2. Signal transduction
3. Polarity

- Proliferation
- Differentiation
- Migration
- Adhesion

Wilson, NEJM, 350 (2), 2004
Pathogenesis

- Abnormal cell proliferation and apoptosis
- Abnormal fluid secretion
- Abnormal cell-matrix interaction and interstitial fibrosis

Wilson, NEJM, 350 (2), 2004
Cell proliferation and apoptosis

EGF:
↑ Concentration
↑ Receptors in apical membrane

hGF
TGF-α
Endothelin
ATP
cAMP
Cytokines
Superoxides
Lipids
(cyst activating factor)

↑ epithelial lining ➔ Cyst formation ➔ hyperplastic polyps and microadenomas
Abnormal fluid secretion

1. Misplacement of Na/K/ATPase in basolateral membranes and Na/K/2Cl symporter in basal surface (B2 isoform)

2. Presence of aquaporine1 and 2 in cyst epithelia

3. Lipid factor (cyst-activating factor)
   \[ \rightarrow (+) \text{cAMP by autocrine or paracrine effect} \]
Cyst fluid secretion

- Glomerular filtrate
- Transepithelial secretion

Granatham, KI, 64, 2003
Abnormal cell-matrix interaction

1. Basement membrane component:
   • Laminin
   • Fibronectin
   • Collagen type IV

   Impact on extrarrenal manifestation
   • MVP
   • Abd wall hernia
   • Intracerebral aneurysm

2. Abnormal interstitium:
   • ↑ Fibroblast growth factor
Normal

ADPKD

ARPKD

Woo, NEJM, 333, 1995
GENETICS

CELL BIOLOGY AND PATHOGENESIS

CLINICAL PICTURE

COMPLICATION

TREATMENT PROSPECTS

OUTCOME

SCREENING & GENETIC COUNSELING
Renal manifestation

Anatomical
Renal cysts (100%)
Renal adenomas (21%)
Cyst calcification

Functional
Concentration abnormality
Citrate excretion (67%)
Impaired renal acidification

Hormonal
↑RAAS
Preserved EPO production

Extrarenal Manifestation

Gastrointestinal
Hepatic cyst (50%, female, aged)
Pancreatic cyst (10%)
Colonic diverticula (80% of ESRD)
Cholangiocarcinoma
Congenital hepatic fibrosis

Cardiovascular
Valvular abnormality (26%)
Intracranial aneurism (5-10%)
Aortic aneurism

Genital
Ovary or testis cysts
Seminal vesicle cysts

Other
Arachnoid cyst
Pineal cyst
Splanic cyst

Hateboer, Clinical Medicine, 3, 2003
First presentation in pediatrics: A 20-year review (n=55)

<table>
<thead>
<tr>
<th>Age at presentation</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>18</td>
</tr>
<tr>
<td>0 to 11 mo</td>
<td>9</td>
</tr>
<tr>
<td>1 to 9y</td>
<td>35</td>
</tr>
<tr>
<td>10 to 18y</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mode precipitating first presentation</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history</td>
<td>53</td>
</tr>
<tr>
<td>Antenatal ultrasound scan</td>
<td>18</td>
</tr>
<tr>
<td>UTI</td>
<td>13</td>
</tr>
<tr>
<td>Abdominal pain or mass</td>
<td>5</td>
</tr>
<tr>
<td>Urinary frequency/dysuria with negative culture</td>
<td>4</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
</tr>
</tbody>
</table>

Tee. AJKD, 43 (2), 2004
First presentation in pediatrics: A 20-year review (n=55)

<table>
<thead>
<tr>
<th>Ultrasound finding at presentation</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral renal cysts</td>
<td>78</td>
</tr>
<tr>
<td>Unilateral renal cysts/right kidney</td>
<td>15</td>
</tr>
<tr>
<td>Unilateral renal cysts/left kidney</td>
<td>7</td>
</tr>
<tr>
<td>Hepatic, splenic or pancreatic cysts</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal function and other parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &lt; 3&lt;sup&gt;rd&lt;/sup&gt; percentile for age</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria&gt; 150mg/d</td>
<td>7</td>
</tr>
<tr>
<td>BP &gt; 95 percentile for age</td>
<td>22</td>
</tr>
<tr>
<td>Elevated cholesterol only</td>
<td>8</td>
</tr>
<tr>
<td>Elevated triglyceride only</td>
<td>35</td>
</tr>
<tr>
<td>Elevated cholesterol and triglyceride</td>
<td>11</td>
</tr>
</tbody>
</table>

Tee. AJKD, 43 (2), 2004
Diagnosis

- Positive family history
- Renal and extrarrenal manifestation
- Image study (to patient or parent)
- DNA linkage analysis:
  - High performance liquid chromatography (HPLC)
  - Single strand conformation polymorphism (SSCP)
## Ultrasonography criteria

<table>
<thead>
<tr>
<th>Age (y/o)</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>at least 2 renal cysts (unilateral or bilateral)</td>
</tr>
<tr>
<td>30-59</td>
<td>at least 2 renal cysts in each kidney</td>
</tr>
<tr>
<td>≥60</td>
<td>at least 4 renal cysts in each kidney</td>
</tr>
</tbody>
</table>

Absent of renal cyst above 30-35y/o almost excludes ADPKD type 1

Ravine, Lancet, 343, 1994
Early stage:
- Small cysts
- Normal renal size
- Normal renal function

ADPKD and ESRD
Chronic hemodialysis

Buturovic-Ponikvar, European J Radiol, 46, 2003
@ Genetics
@ Cell biology and pathogenesis
@ Clinical picture
@ Complication
@ Treatment prospects
@ Outcome
@ Screening & genetic counseling
Complications

- HTN (>80% adult, 20-30% child)
- Acute and chronic pain (60% adult, 20% child)
- UTI
- Hematuria (50% adult, 10% child)
- Nephrolithiasis (20-34%)
- Cyst rupture
- Hepatomegaly (20-30% over age 50, female)
- Intracranial aneurysm rupture
- Renal failure (50% by age of 60, age dependent)
Hypertension and ADPKD

1. Renal vascular ischemia by local tubular compression
   - Activation of RAAS
   - Activation of sympathetic system
   - Release of endothelin

2. Abnormal proximal cell sodium handling
3. ↑ ANP
4. NO deficiency

- Plasma volume
- Sodium retention
- ↑ Cardiac index
- LVH

- Renal progression
- Cardiovascular mortality

Neumann, Curr Opin nephrol Hyper, 11(5), 2002
Intracranial aneurysm (ICA) rupture

- Mean age for ICA rupture: 41 y/o
- Average rate of rupture: 2%
- **Risk factor:** positive family history of ICA rupture or SAH
- No clear association to age, gender, HTN, renal function
- Location: same as general population (Anterior circulation, MCA)

Belz, KI, 63, 2003
Screening of intracranial aneurysm rupture

- Age 18-55 y/o + positive family history of ICA
  - no → No screening
  - yes → Brain MRI or spiral CT scan
    - no → Repeat every 5 years
    - yes → Conventional angiography
      - If > 1 cm → Surgical intervention

Gibbs, KI, 65, 2004
### Table 2-1. Taiwan's End-Stage Renal Disease Rate by Age, Sex, and Etiology

<table>
<thead>
<tr>
<th>Age Group</th>
<th>88 Population</th>
<th>88 Incident</th>
<th>Percent</th>
<th>Rate per 1,000,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>6,674,848</td>
<td>232</td>
<td>0.86</td>
<td>35</td>
</tr>
<tr>
<td>20-44</td>
<td>9,411,444</td>
<td>5,385</td>
<td>19.85</td>
<td>572</td>
</tr>
<tr>
<td>45-64</td>
<td>4,140,623</td>
<td>12,012</td>
<td>44.28</td>
<td>2,901</td>
</tr>
<tr>
<td>65-74</td>
<td>1,229,338</td>
<td>6,507</td>
<td>23.99</td>
<td>5,293</td>
</tr>
<tr>
<td>75+</td>
<td>636,134</td>
<td>2,989</td>
<td>11.02</td>
<td>4,699</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>88 Population</th>
<th>88 Incident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11,312,728</td>
<td>12,827</td>
</tr>
<tr>
<td>Female</td>
<td>10,779,659</td>
<td>14,315</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**Average Age**

- Male: 57.0 ± 14.8
- Female: 57.0 ± 15.3

**Etiology**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Glomerulonephritis (CGN)</td>
<td>11,433</td>
<td>42.12</td>
</tr>
<tr>
<td>Toxemic Nephropathy (TIN)</td>
<td>443</td>
<td>1.63</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,406</td>
<td>5.18</td>
</tr>
<tr>
<td>Diabetic Mellitus (DM)</td>
<td>6,022</td>
<td>22.19</td>
</tr>
<tr>
<td>Gout</td>
<td>353</td>
<td>1.30</td>
</tr>
<tr>
<td>Cystic Kidney Disease</td>
<td>435</td>
<td>1.60</td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>140</td>
<td>0.52</td>
</tr>
<tr>
<td>Stone</td>
<td>295</td>
<td>1.09</td>
</tr>
<tr>
<td>Unknown</td>
<td>6,616</td>
<td>24.37</td>
</tr>
</tbody>
</table>

**Total**

- 27,143
- 100.0%
- 1,241

*USRDS, 2002*

- 4th leading cause of ESRD
- Male
- African-Americans

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*Source: Data from the Taiwan National Health Insurance Program*
Risk factors for progressive renal disease in ADPKD

- Younger age at diagnosis
- Race (black and sickle cell trait)
- Male gender
- Genetic abnormality (PKD1 gene)
- Gross hematuria
- Hypertension
- Increased renal size

Fick-Brosnahan, AJKD, 39, 2002
ADPKD and renal failure

Cause:

- Tissue compression
- Vascular sclerosis
- Interstitial fibrosis
- Cell apoptosis
Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort

241 patients (15-45y/o)

- Renal volume
- Cyst volume
- Hypertension
- Urinary Alb excretion

Correlate with GFR

Chapman, KI, 64, 2003
@ Genetics
@ Cell biology and pathogenesis
@ Clinical picture
@ Complication
@ Treatment prospects
@ Outcome
@ Screening & genetic counseling
Treatment prospective

Antimutagens
- Inhibitors of phase I enzymes (e.g., p-XS2)
- Inducers of phase II enzymes (e.g., olitipraz)

Antioxidants
- e.g., vitamin E/selenium, Probucol, NAC

Somatic mutation(s)

Metabolic interventions
- Protein restriction
- Soy protein/flax seed
- Bicarbonate/citrate

Growth factors (TGF-α, "EGF", PDGF, TGF-β, aFGF, bFGF, IGF-1)
Chemokines (IL-8, MCP-1) and osteoponitin
Cytokines (TNF-α, IL-1, IL-2, IL-6)
ATP, cAMP
Bioactive lipids (CAF, lactosylceramide)
MMPs, TIMPs, and lysosomal enzymes
Renin, endothelin

Epithelial cell proliferation
Apoptosis

Fluid secretion

Interstitial inflammation
Matrix accumulation

Tubular obstruction
Angiosclerosis

Signal transduction modulators
- ErbB TK inhibitors
- Ras inhibitors
- PKA type 1 inhibitors
- Other effector kinase inhibitors
- Retinoids and vitamin D

Hormone/autooid modulators
- AVP-V2 receptor antagonist
- Somatostatin

Anti-inflammatory agents
- Glucocorticoids
- COX-2 inhibitors
- LOX inhibitors
- TACE inhibitors
- MMP inhibitors

ACE inhibitors
- AT1 antagonists
- Endothelin antagonists
- Nitric oxide

Qi Qian, KI, 63, 2001
Treatment of HTN in ADPKD

- ACE inhibitor
- Calcium channel blocker
- AT-II antagonist
- Diuretics
- Lovastatin
- Dilazep dihydrochloride
- Ammonium chloride (bicarbonate)

Neumann, Curr Opin nephrol Hyper, 11(5), 2002
ACEI and survival of ADPKD after ESRD

Hypertensive males:
N=81 vs 61
MAP: 109 vs 102
DBP: 94 vs 85
ACEI:16.1% vs 54.1
(P<0.0001)

Hypertensive females:
N=96 vs 108  p<0.0001
MAP: 101 vs 99  p=0.038
DBP: 87 vs 82  p<0.0001
ACEI:13.5% vs 48.2%  
(p<0.0001)

Schrier, KI, 63,2003
No effect of enalapril in normotensive ADPKD patients

<table>
<thead>
<tr>
<th></th>
<th>Enalapril (n=32)</th>
<th>Placebo (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>103 ± 2</td>
<td>103 ± 1</td>
<td>0.67</td>
</tr>
<tr>
<td>after 3 years follow-up</td>
<td>100 ± 2</td>
<td>105 ± 3</td>
<td>0.22</td>
</tr>
<tr>
<td>decrease</td>
<td>−3 ± 2</td>
<td>2 ± 2</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>106 ± 4</td>
<td>112 ± 3</td>
<td>0.34</td>
</tr>
<tr>
<td>after 3 years follow-up</td>
<td>97 ± 5</td>
<td>105 ± 5</td>
<td>0.25</td>
</tr>
<tr>
<td>decrease</td>
<td>9 ± 1*</td>
<td>−7 ± 3*</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Effective renal plasma flow (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>437 ± 24</td>
<td>439 ± 21</td>
<td>0.94</td>
</tr>
<tr>
<td>after 3 years follow-up</td>
<td>393 ± 22</td>
<td>406 ± 22</td>
<td>0.73</td>
</tr>
<tr>
<td>decrease</td>
<td>−44 ± 11</td>
<td>−33 ± 11</td>
<td>0.09</td>
</tr>
</tbody>
</table>

van Dijk, NDT, 18, 2003
No effect of enalapril in hypertensive ADPKD patients

<table>
<thead>
<tr>
<th></th>
<th>Enalapril (n=13)</th>
<th>Atenolol (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>113±2</td>
<td>108±2</td>
<td>0.06</td>
</tr>
<tr>
<td>at 3 years follow-up</td>
<td>102±3</td>
<td>105±2</td>
<td>0.53</td>
</tr>
<tr>
<td>decrease</td>
<td>-11±3*</td>
<td>-3±3*</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>80±9</td>
<td>92±9</td>
<td>0.32</td>
</tr>
<tr>
<td>at 3 years follow-up</td>
<td>64±9</td>
<td>83±8</td>
<td>0.13</td>
</tr>
<tr>
<td>decrease</td>
<td>-12±2**</td>
<td>-12±3**</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Effective renal plasma rate (ml/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>316±127</td>
<td>378±138</td>
<td>0.24</td>
</tr>
<tr>
<td>at 3 years follow-up</td>
<td>249±127</td>
<td>311±144</td>
<td>0.26</td>
</tr>
<tr>
<td>decrease</td>
<td>-67±47</td>
<td>-67±38</td>
<td>0.99</td>
</tr>
</tbody>
</table>

van Dijk, NDT, 18, 2003
# Therapeutic strategies to retard progression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihypertensive agent</strong></td>
<td></td>
</tr>
<tr>
<td>Enalapril/losartan</td>
<td>yes?</td>
</tr>
<tr>
<td>ACEI</td>
<td></td>
</tr>
<tr>
<td>+ diuretics</td>
<td>no</td>
</tr>
<tr>
<td>+ CCB</td>
<td>no</td>
</tr>
<tr>
<td>+ other</td>
<td>no</td>
</tr>
<tr>
<td><strong>Dietary manipulation</strong></td>
<td></td>
</tr>
<tr>
<td>Protein restriction</td>
<td>yes/no</td>
</tr>
<tr>
<td>Soy protein</td>
<td>yes</td>
</tr>
<tr>
<td>Fish oil</td>
<td>no</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid-lowering therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>yes</td>
</tr>
<tr>
<td>Probucol</td>
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</tr>
<tr>
<td>α-tocopherol</td>
<td>no</td>
</tr>
<tr>
<td><strong>Other</strong></td>
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</tr>
<tr>
<td>Taxanes</td>
<td>yes/no</td>
</tr>
<tr>
<td>Potassium citrate</td>
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</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>no</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>no</td>
</tr>
</tbody>
</table>

Davis, Semin Nephrol, 21(5), 2001
Pain in ADPKD

- 60% of ADPKD patients
- Acute pain:
  - Infected cysts
  - Cyst rupture/hemorrhage (>15cm, HTN)
  - Nephrolithiasis (uric acid stone, hypocitraturia)
- Chronic pain:
  - Mechanical back pain
  - Cyst enlargement
  - Hepatomegaly
- Headache pain
Pain control: step-ladder approach

→ Non-pharmacologic
   • Behavioral modification
   • Ice/heat pad
   • Alexander technique

→ Systemic analgesics
   • Acetaminophen
   • Salsalate
   • NSAIDs
   • Cox-2 inhibitor
   • Tramadol
   • Clonidine

→ Low dose opioids

→ Transcutaneous electrical nerve stimulation/acupuncture

→ Spinal cord stimulation/neuraxial opioids and local anesthetics
   • Decompression
   • Decortication
   • Hepatectomy
   • Renal denervation
   • Nephrectomy

→ Surgical approach (liver/kidney)

Bajwa, KI, 60 (5), 2001
Genetics

Cell biology and pathogenesis

Clinical picture

Complication

Treatment prospects

Outcome

Screening & genetic counseling
Death in ADPKD

Perrone, AJKD, 38(4), 2001
Survival of ADPKD after ESRD

Perrone, AJKD, 38(4), 2001
Death from extrarrenal manifestation

<table>
<thead>
<tr>
<th></th>
<th>No. Patients</th>
<th>No. Deaths per 1,000 Patient-Years</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ADPKD</td>
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<tr>
<td>N</td>
<td>9,435</td>
<td>9,435</td>
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<tr>
<td>Deaths from all causes</td>
<td>3,414</td>
<td>2,054</td>
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<tr>
<td>Deaths from extrarenal manifestations</td>
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<tr>
<td>Polycystic liver disease (item 68, HCFA 2746) or cirrhosis (item 67, HCFA 2746) or liver failure, cause unknown other (item 69, HCFA 2746)</td>
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<td>Polycystic liver disease (item 68, HCFA 2746)</td>
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<td>Cardiac valvular disease (item 30, HCFA 2746)</td>
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<td>Cerebrovascular disease including intracranial hemorrhage (item 36, HCFA 2746)</td>
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<td>112</td>
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<td>Perforation of bowel (not peptic ulcer) (item 76, HCFA 2746) (diverticular disease)</td>
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<td>25</td>
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<tr>
<td>Hemorrhage from ruptured vascular aneurysm (item 41, HCFA 2746)</td>
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</tbody>
</table>

Perrone, AJKD, 38(4), 2001
@ Genetics
  @ Cell biology and pathogenesis
    @ Clinical picture
      @ Complication
        @ Treatment prospects
          @ Outcome
            @ Screening & genetic counseling
Each child of affected person has 50% chance to inheriting the disease gene!

When

How

Screening and Genetic counseling

Especial clinical conditions??
• Genetic counseling and medical ethics

• Antenatal screening:
  - Prenatal ultrasound: Renal cyst, Oligohydramnios
  - DNA linkage analysis: Chorionic villus sampling

• Adult with positive family history, a negative ultrasonographic finding after 30 y/o excludes the disease
Screening tools

- Renal ultrasound (choice)
- CT scan or MRI
- DNA linkage analysis:
  - High performance liquid chromatography (HPLC)
  - Single strand conformation polymorphism (SSCP)
Especial conditions....

1. Incidental finding of renal cysts
   Unknown family history:
   → Ultrasound evaluation to both parents

2. Positive family history, < 30y/o, potential renal donor
   → CT scan or MRI
   → DNA linkage analysis

Serial follow up of renal ultrasound!!!
Germline mutations
- PKD1 gene
- PKD2 gene

Somatic mutations
- Family history
- Screening

Modifying genes
- BP control
- Diet manipulation
- Lipid lowering
- EGFR antagonist?

Cell proliferation
Apoptosis
Fluid secretion
Matrix interaction

Cyst Initiation

Cyst enlargement

Environmental factors

Progression