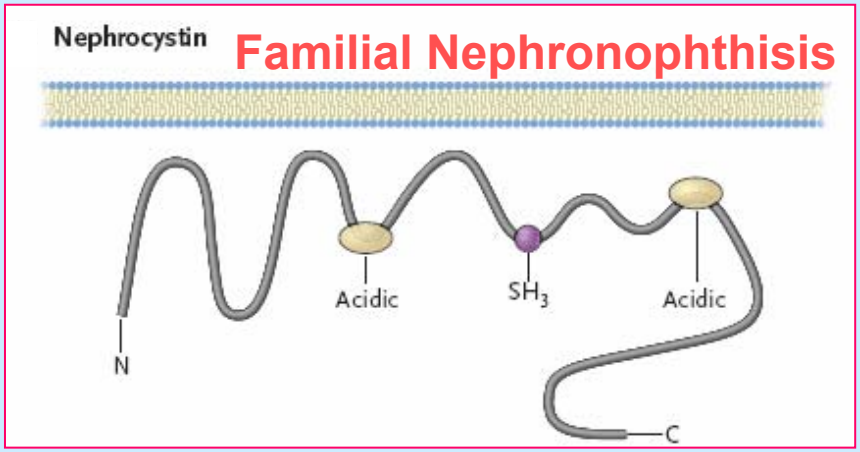
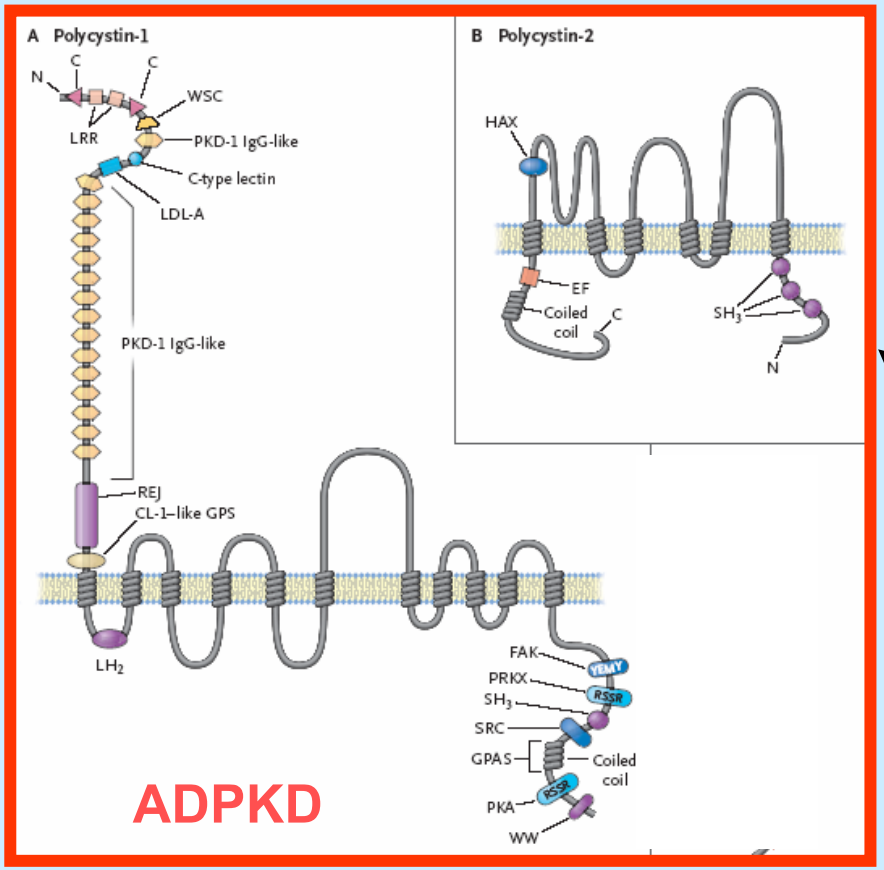
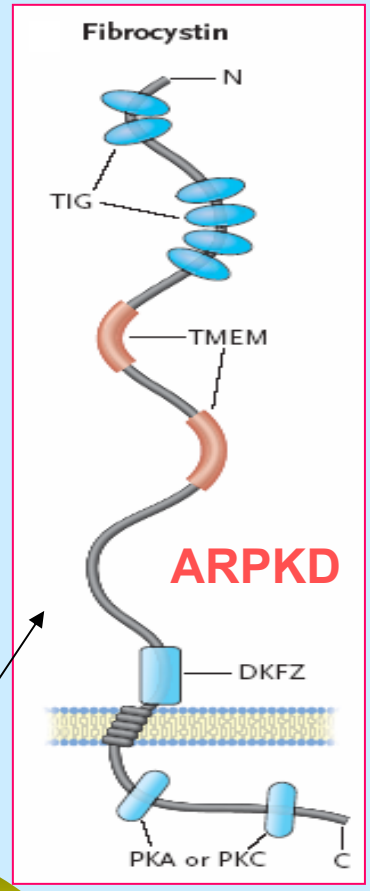
Fellow Seminar

Autosomal Dominant Polycystic Kidney Disease

F2 吳逸文醫師, 25/08/2004







Polycystic Kidney Disease

@ Genetics

@ Cell biology and pathogenesis

@ Clinical picture

@ Complication

@Treatment prospects

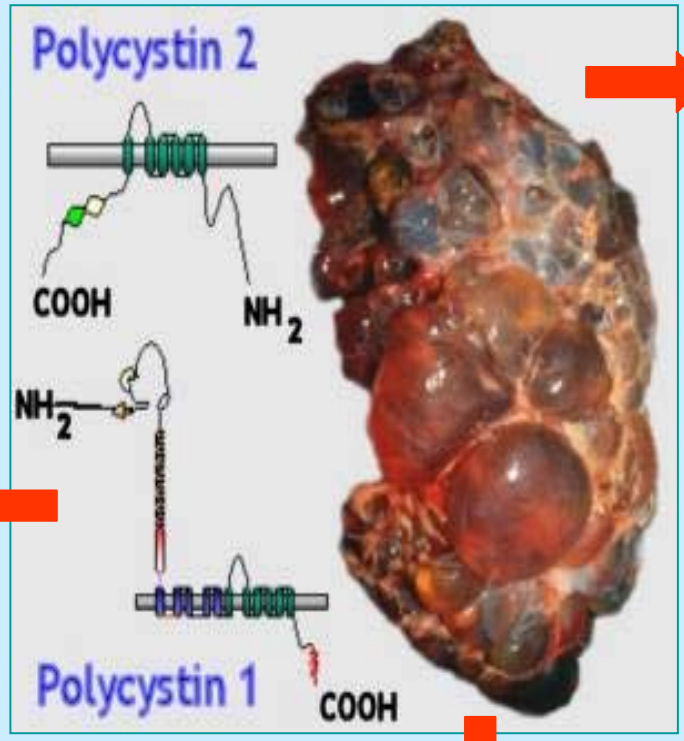
@ Outcome

@ Screening & genetic counseling

PKD1 vs PKD2 genes

***PKD1* gene 16p13.3**
(1994,1995):
•46 exons
•4302 amino acids
•**Distribution:**
kidney
(distal nephron and collecting duct)
brain
heart
bone
muscle

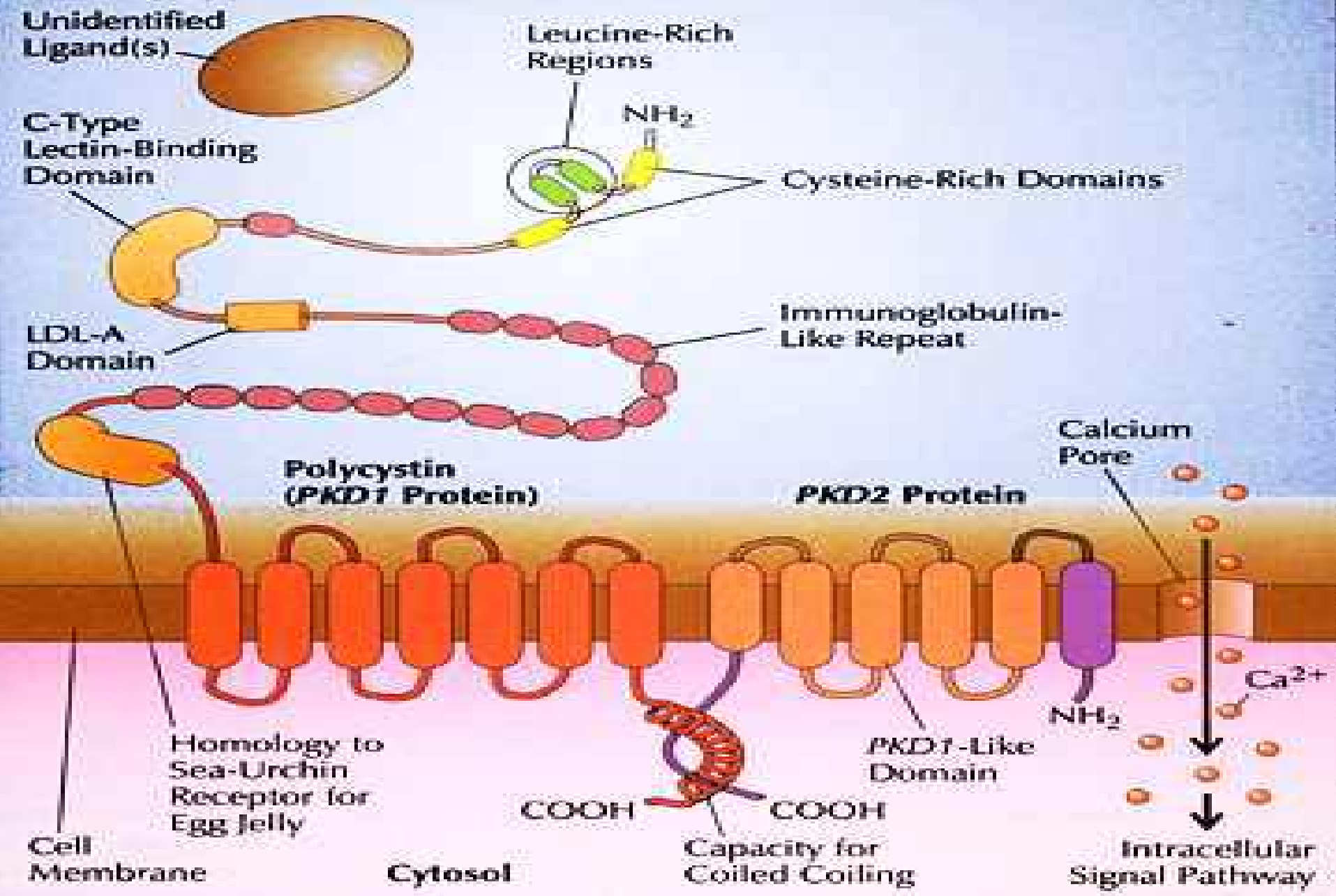
•**Mutations: (85%)**
splite site, in-frame, out-frame
deletion or insertion
non-sense mutation



***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

Unknown *PKD3* gene?
short arm of Chro 7


Unidentified Ligand(s)
Leucine-Rich Regions
NH_2
C-Type Lectin-Binding Domain
Cysteine-Rich Domains
LDL-A Domain
Immunoglobulin-Like Repeat
Calcium Pore
Polycystin (*PKD1* Protein)
PKD2 Protein
Ca^{2+}
NH_2
Homology to Sea-Urchin Receptor for Egg Jelly
PKD1-Like Domain
COOH
COOH
Capacity for Coiled Coiling
Cell Membrane
Cytosol
Intracellular Signal Pathway

ADPKD is a focal disease?
"Two-hit hypothesis"

germline mutated PKD1
(or PKD2) allele

Somatic mutation

wild-type gene

Inactive the gene
Initiate cyst formation

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

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

Note: Values expressed as mean ± SD

Chang MY, CGMH, poster of TSN, 2003

Mutations in the PKD2 gene in 3 patients (15%)

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

Chang MY, CGMH, poster of TSN, 2003

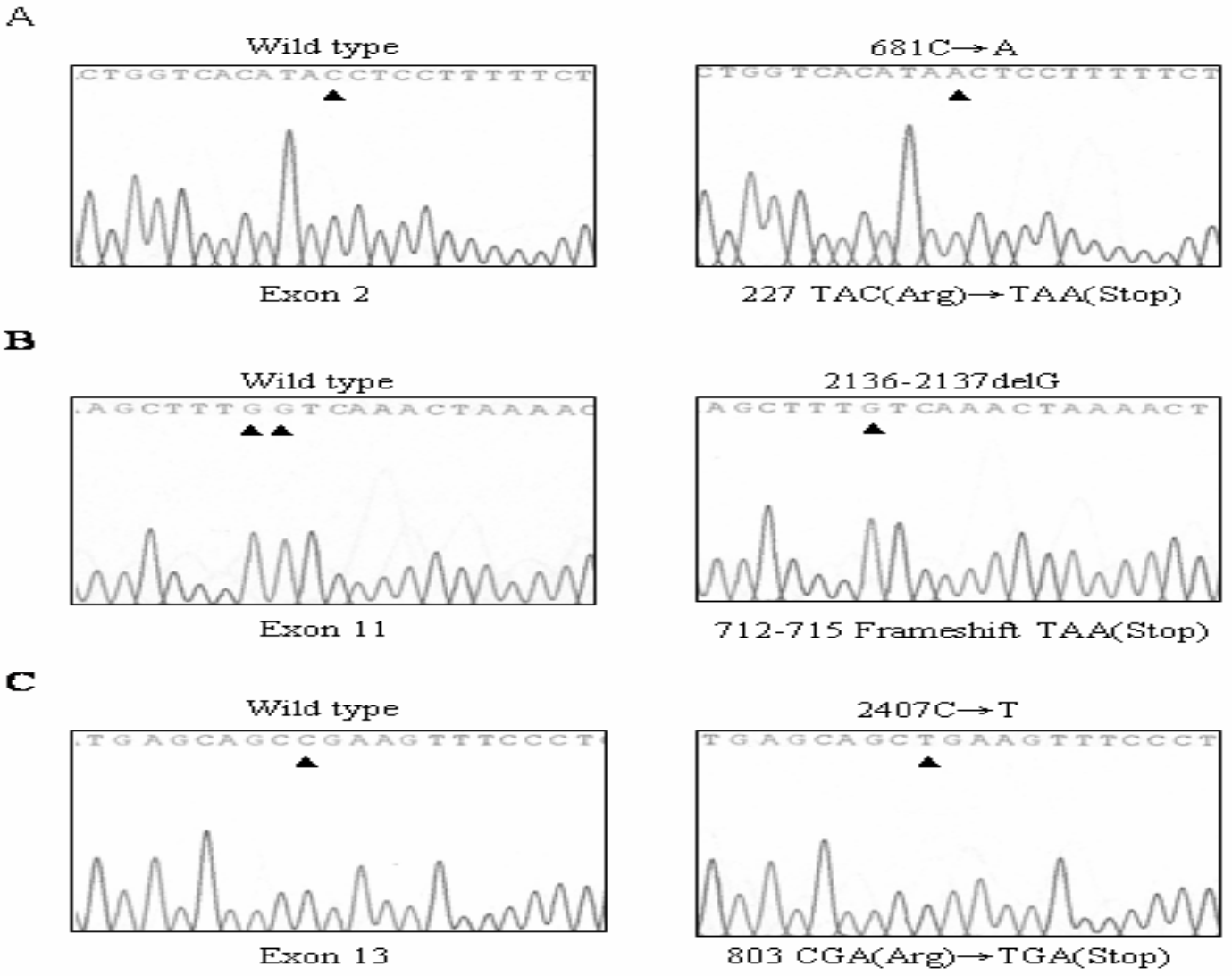
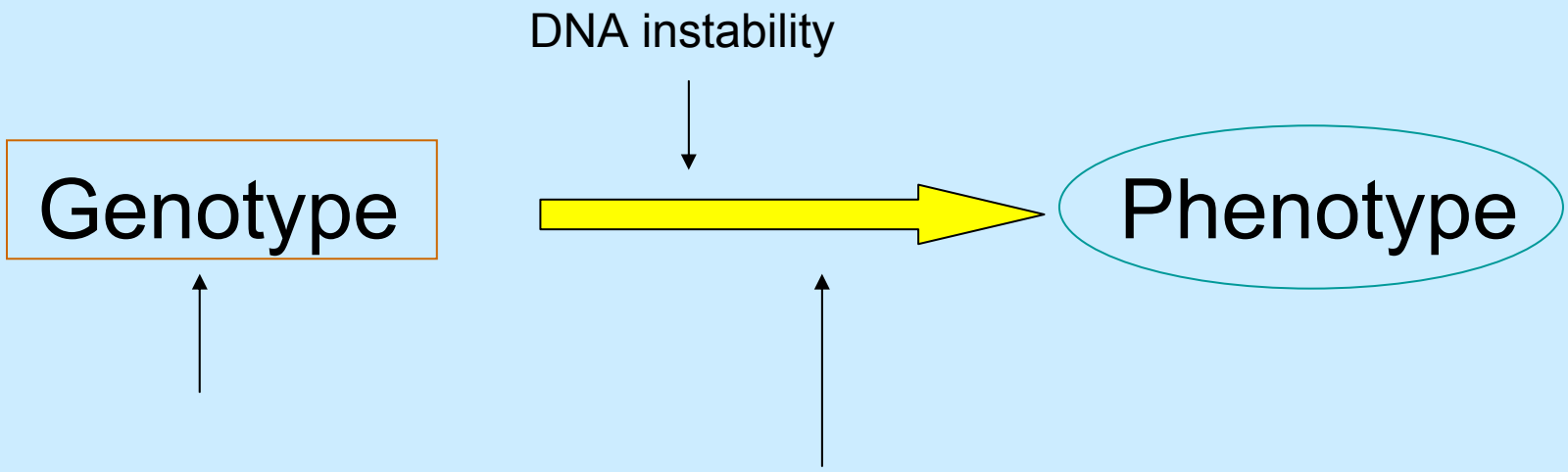


Figure 1 :Sequence data showing three PKD2 gene mutations:
(A) Nonsense mutation Y227X; C681A; (B):Frameshift mutation 712-715 X; 2136-2137delG
(C) Nonsense mutation R803X; C2407T.

Interfamilial and intrafamilial heterogenecity…modifier gene?



Devuyst, NDT, 18, 2003

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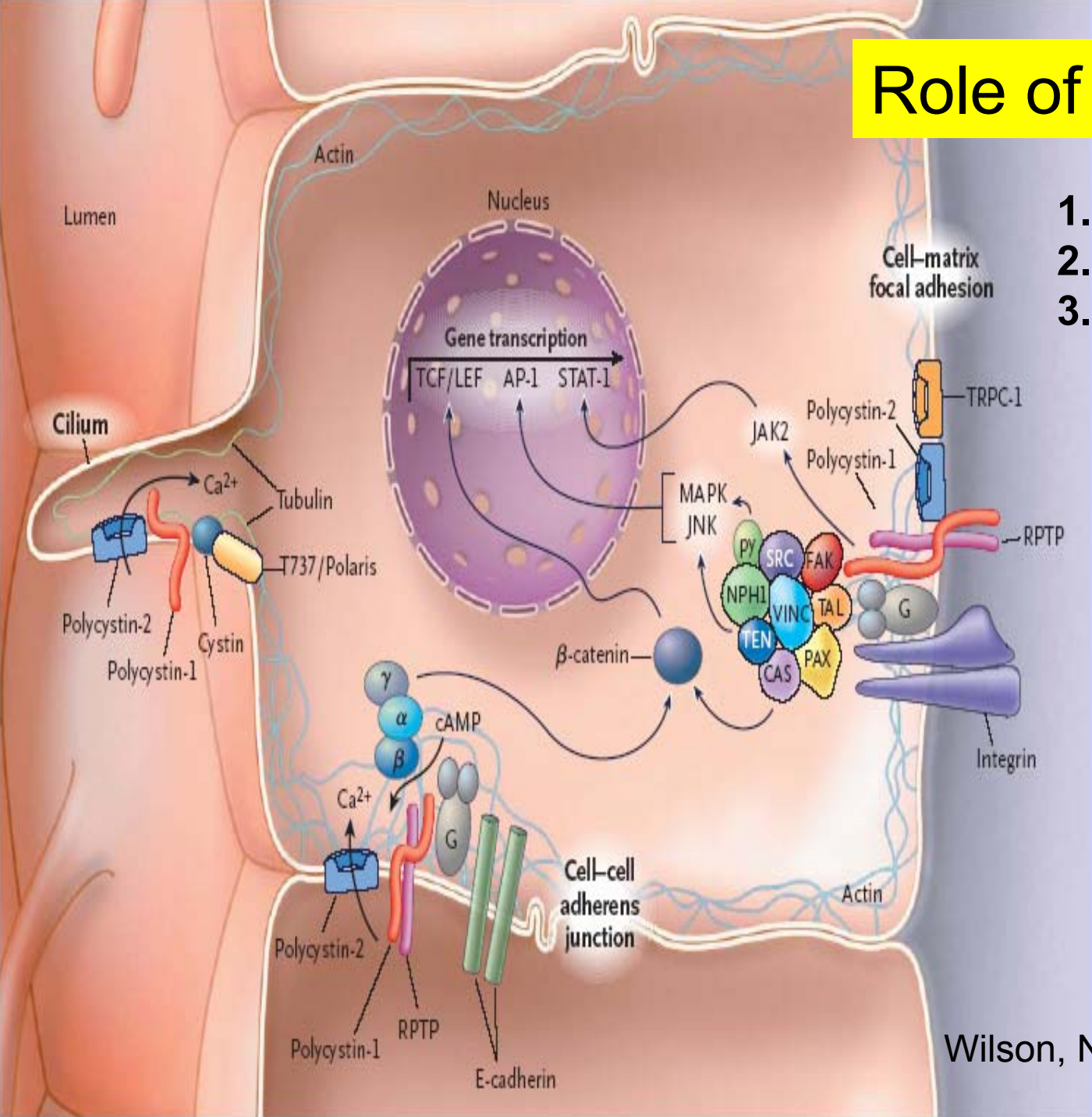
Role of polycystins:



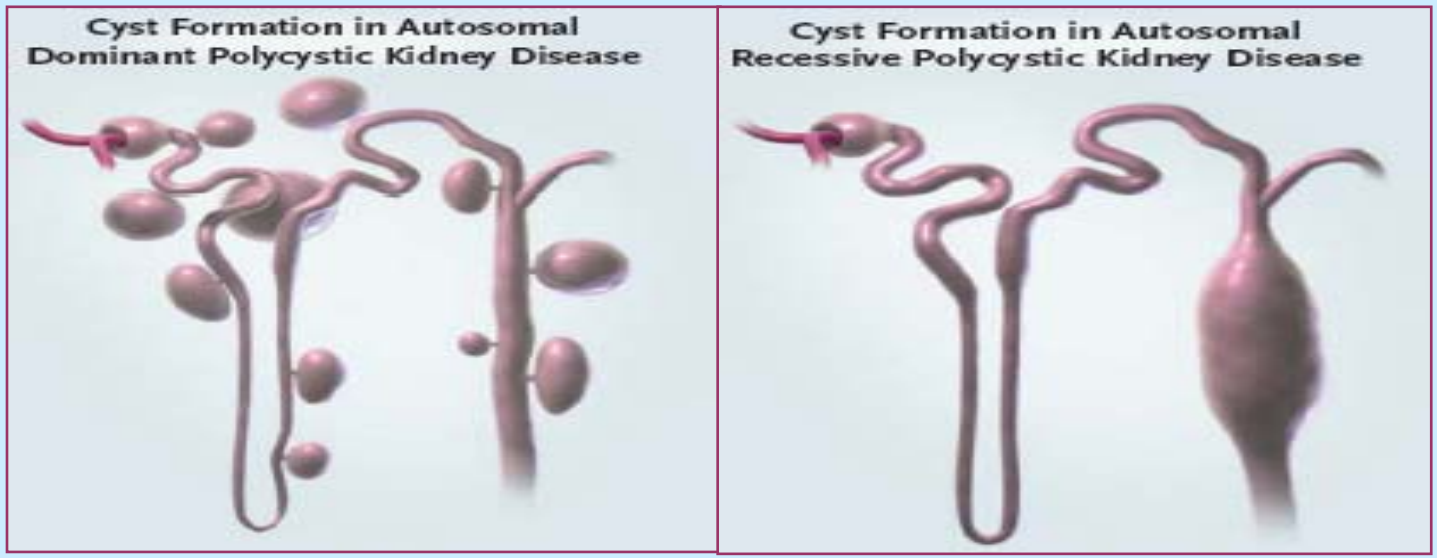
1. Mechanoreceptor
2. Signal transduction
3. Polarity

- Proliferation
- Differentiation
- Migration
- Adhesion

Wilson, NEJM, 350 (2), 2004

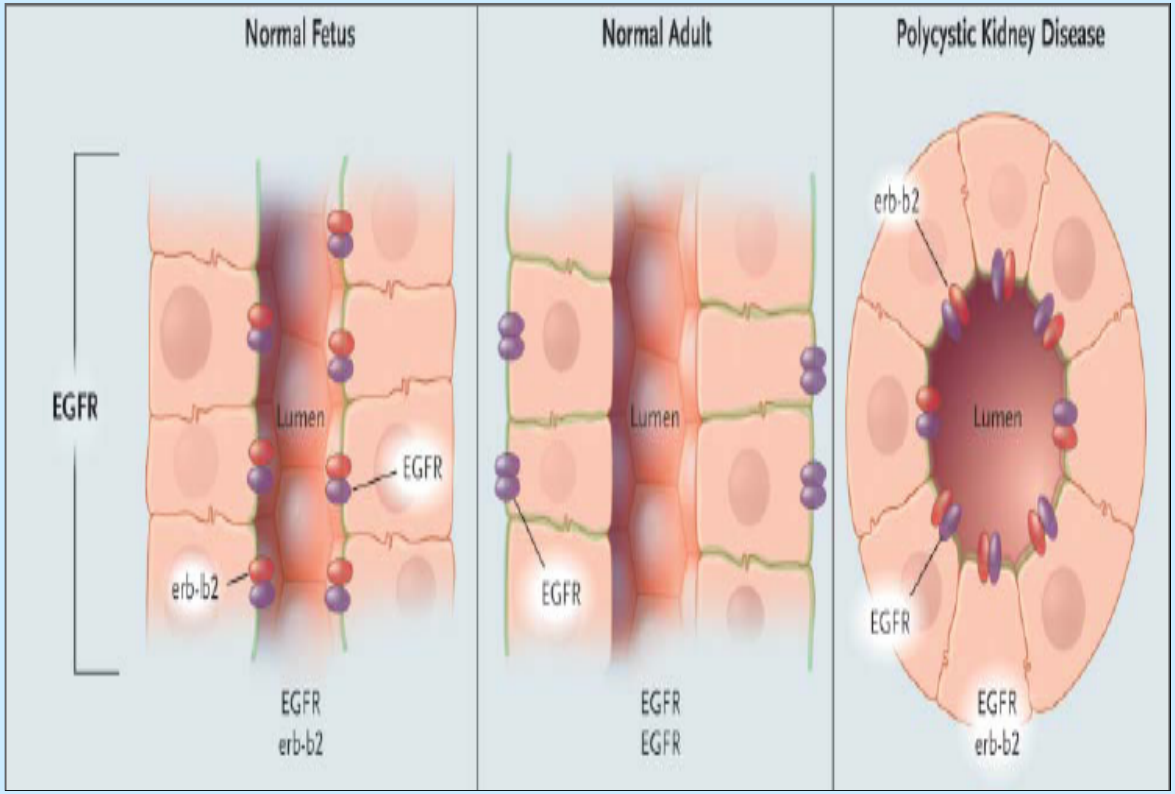
Pathogenesis

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



Wilson, NEJM, 350 (2), 2004

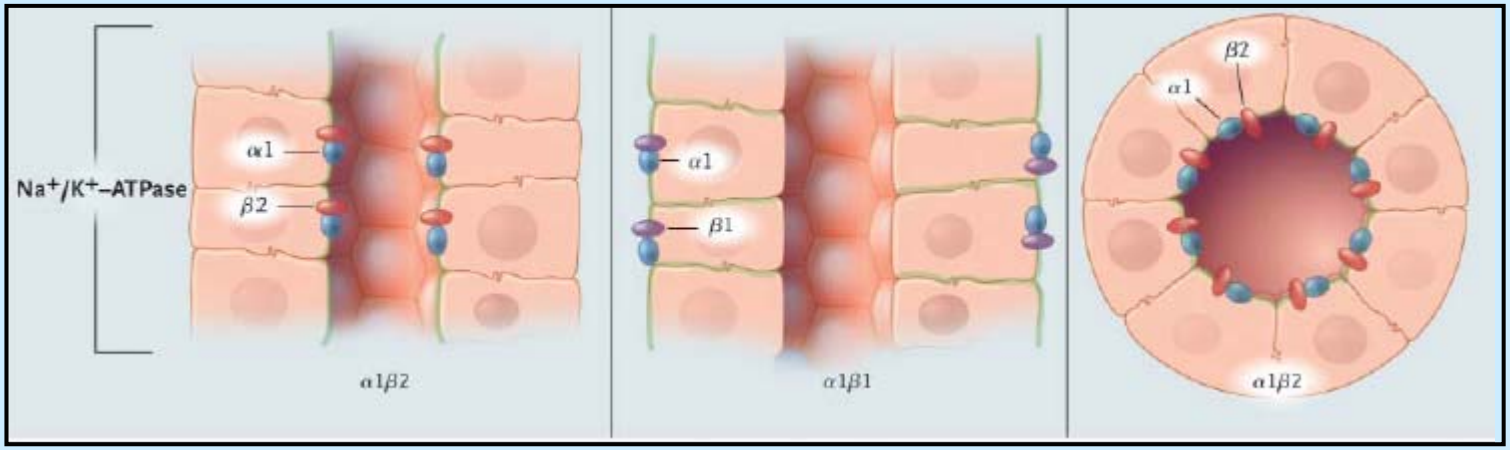
Cell proliferation and apoptosis



EGF:
↑ Concentration
↑ Receptors in apical membrane
hGF
TGF-α
Endothelin
ATP
cAMP
Cytokines
Superoxides
Lipids
(cyst activating factor)

↑ epitheliar lining→ Cyst formation → hyperplastic polyps and microadenomas

Abnormal fluid secretion



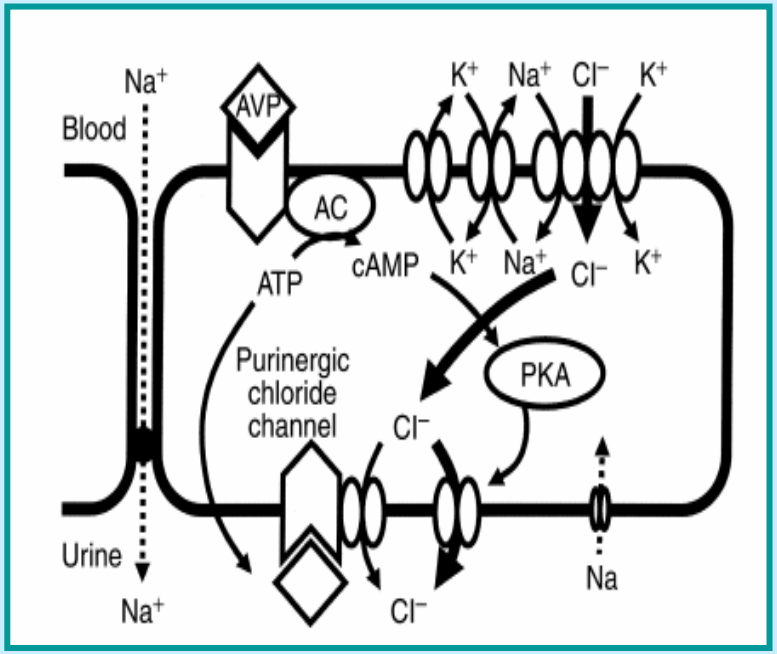
1. Misplacement of Na/K/ATPase in basolateral membranes and Na/K/2Cl symporter in basal surface (B2 isoform)

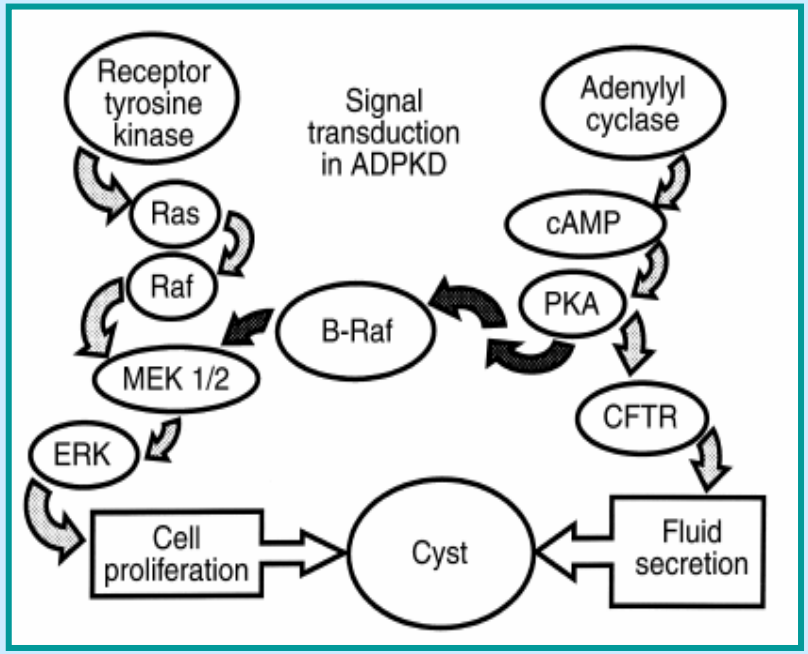
2. Presence of aquaporine1 and 2 in cyst epithelia

3. Lipid factor (cyst-activating factor)
   → (+) cAMP by autocrine or paracrine effect

Cyst fluid secretion

- Glomerular filtrate
- Transepitheliar secretion





Grantham, KI, 64, 2003

Abnormal cell-matrix interaction

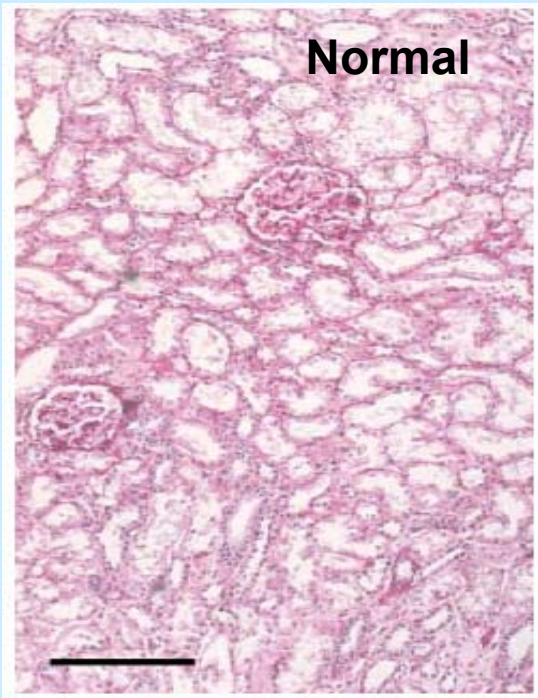
1. Basement membrane component:

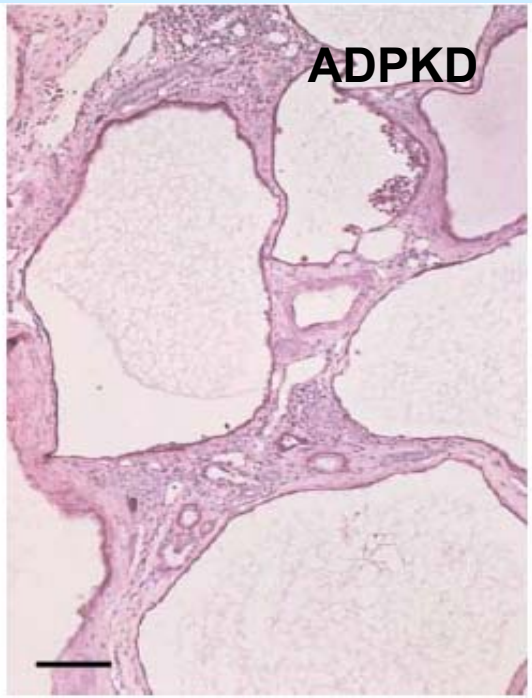
- Laminin
- Fibronectin
- Collagen type IV

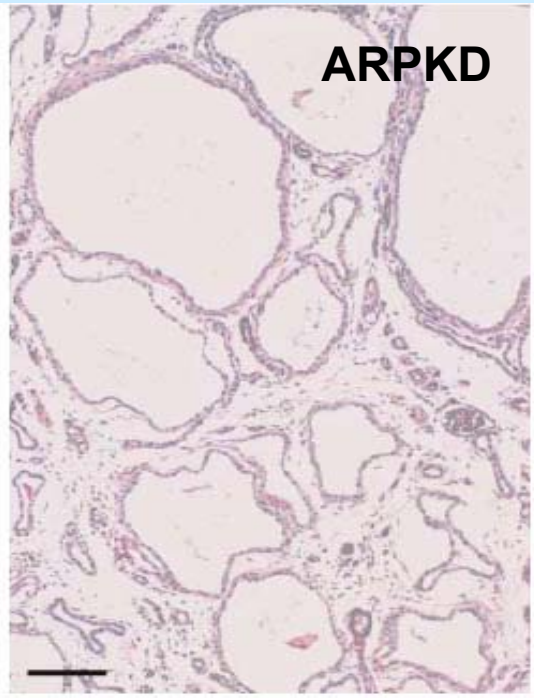
Impact on extrarrenal manifestation
- MVP
- Abd wall hernia
- intracerebral aneurysm

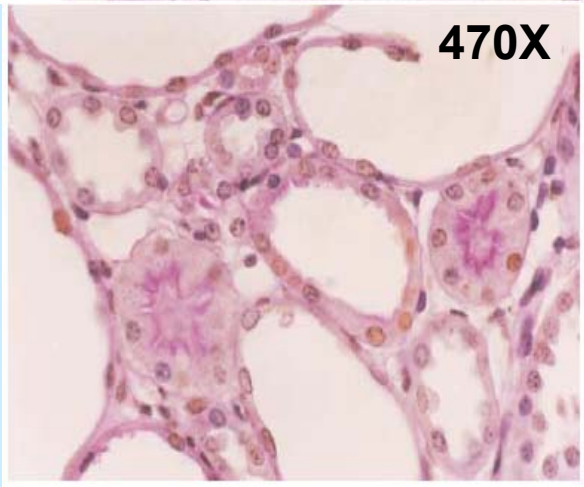
2. Abnormal interstitium:

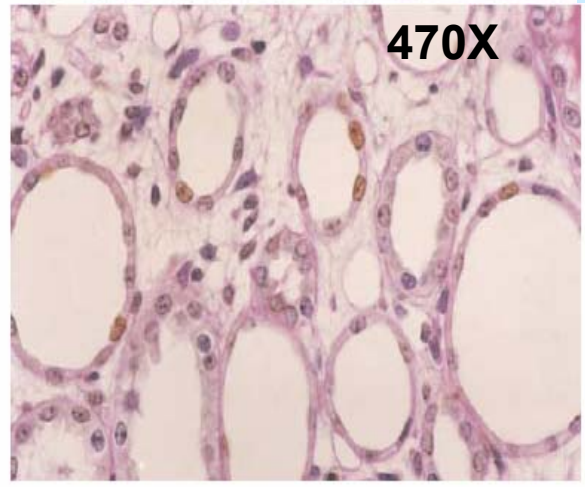
- ↑ Fibroblast growth factor



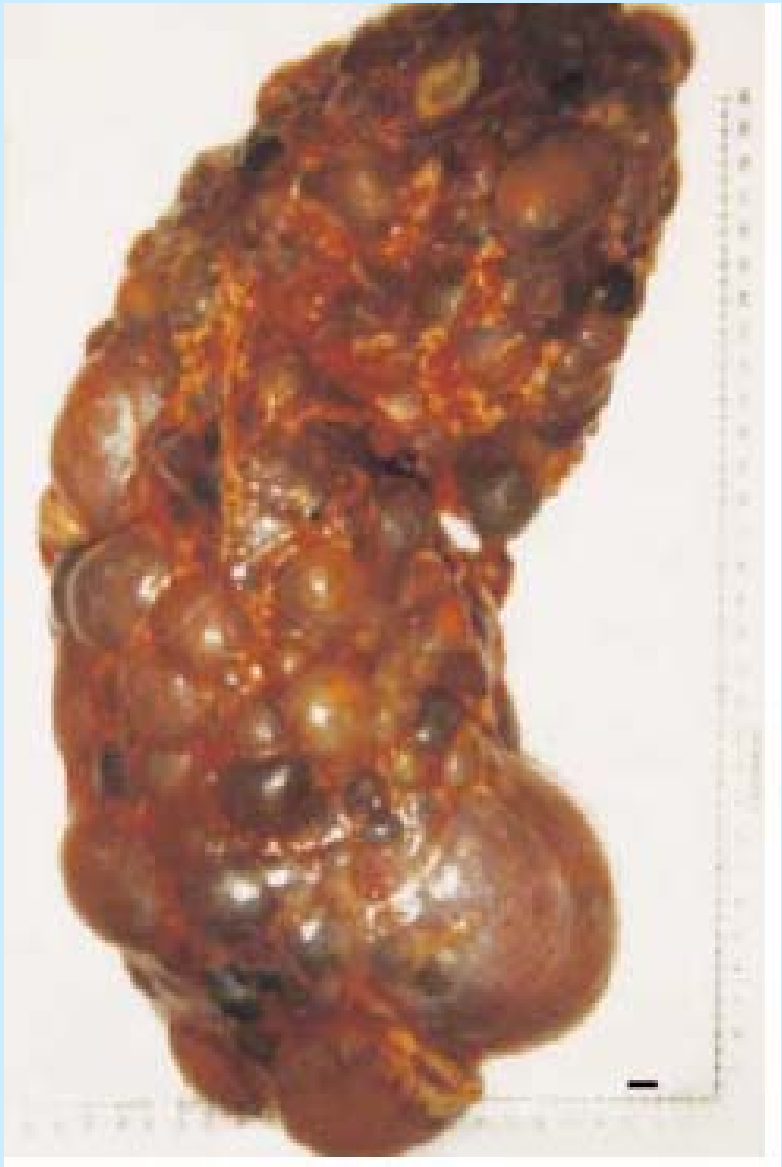


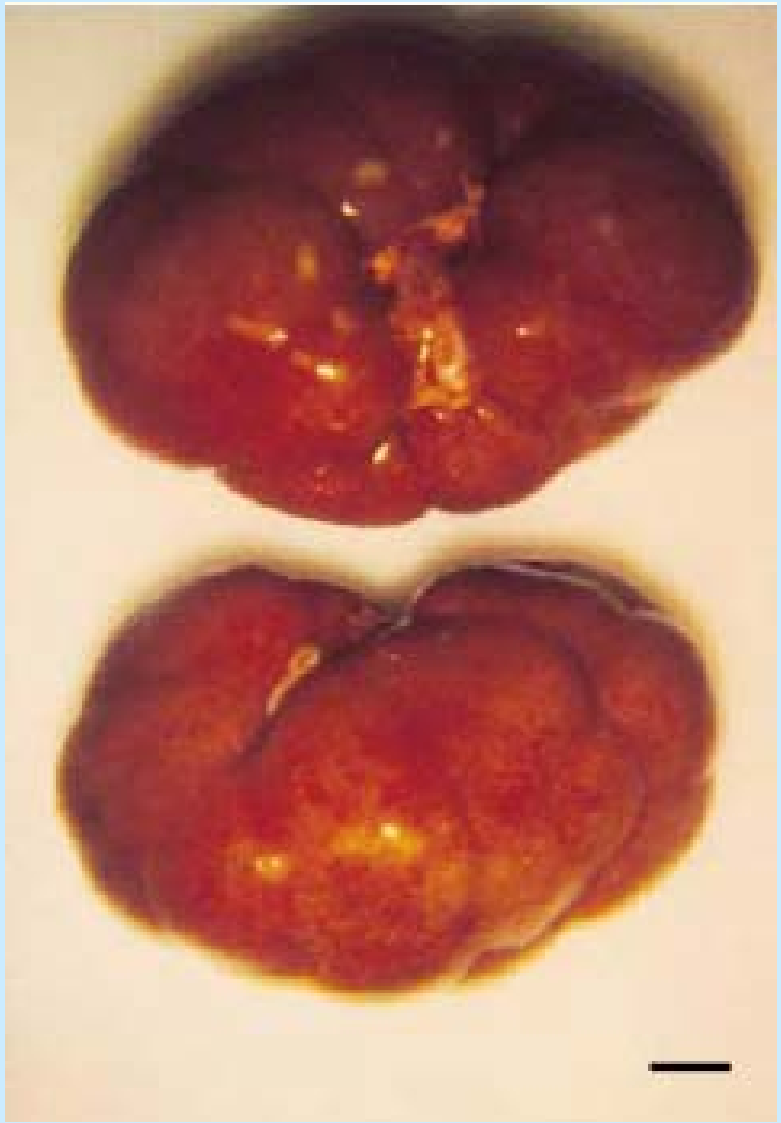






Woo, NEJM,333,1995





Woo, NEJM,333,1995

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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 aneurysm

Genital
- Ovary or testis cysts
- Seminal vesicle cysts

Other
- Arachnoid cyst
- Pineal cyst
- Splenic cyst

Hateboer, Clinical Medicine, 3, 2003

First presentation in pediatrics: A 20-year review (n=55)

Age at presentation	% of patients
Prenatal	18
0 to 11 mo	9
1 to 9y	35
10 to 18y	38
Mode precipitating first presentation	
Positive family history	53
Antenatal ultrasound scan	18
UTI	13
Abrominal pain or mass	5
Urinary frequency/dysuria with negative culture	4
Gross hematuria	2
Miscellaneous	5

Tee. AJKD, 43 (2), 2004

First presentation in pediatrics: A 20-year review (n=55)

Ultrasound finding at presentation	**% of patients**
Bilateral renal cysts	78
Unilateral renal cysts/right kidney	15
Unilateral renal cysts/left kidney	7
Hepatic, splenic or pancreatic cysts	0
Renal function and other parameters	
GFR < 3rd percentile for age	2
Proteinuria> 150mg/d	7
BP > 95 percentile for age	22
Elevated cholesterol only	8
Elevated triglyceride only	35
Elevated cholesterol and triglyceride	11

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)

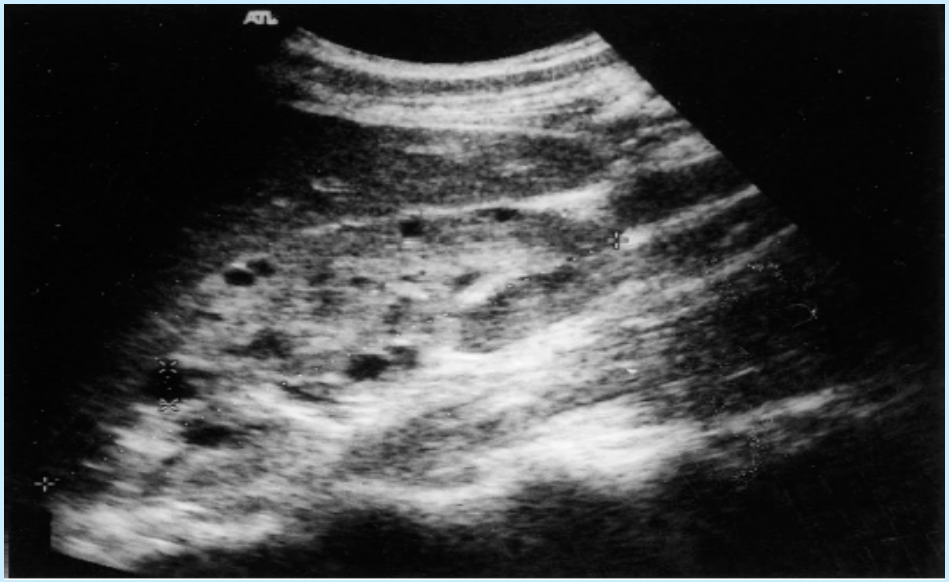
Single strand conformation polymorphism (SSCP)

Ultrasonography criteria

Age(y/o)	Criteria
<30	at least 2 renal cysts (unilateral or bilateral)
30-59	at least 2 renal cysts in each kidney
≥60	at least 4 renal cysts in each kidney

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

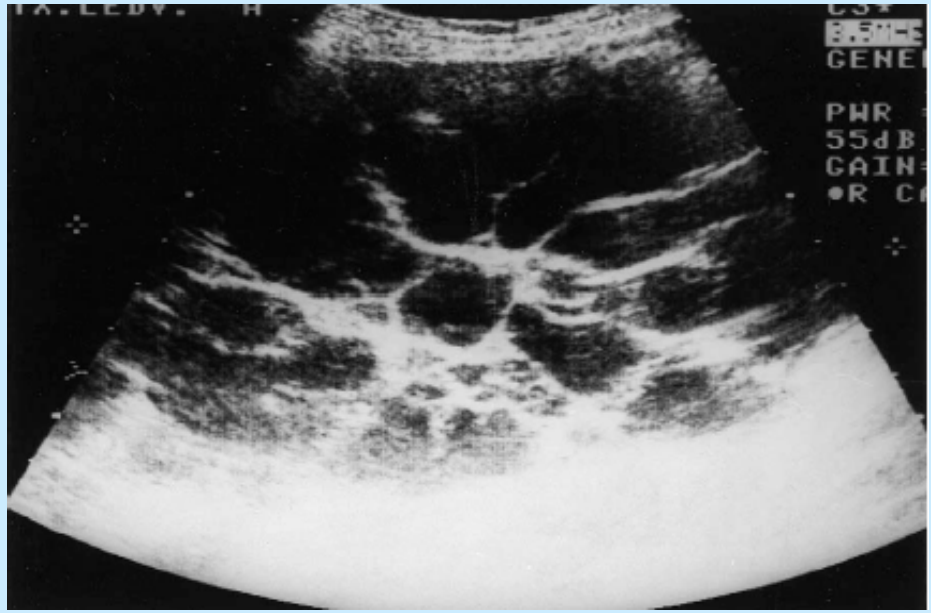
Ravine, Lancet, 343, 1994



Early stage:

- Small cysts
- Normal renal size
- Normal renal function

ADPKD and ESRD
Chronic hemosdialysis



Buturovic-Ponikvar, European J Radiol,46, 2003

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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)
- Intracraneal aneurysm rupture
- Renal failure (50% by age of 60, age dependent)

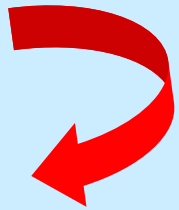
Hypertension and ADPKD

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 retension
- ↑Cardiac index
- LVH



- Renal progression
- Cardiovascular mortality

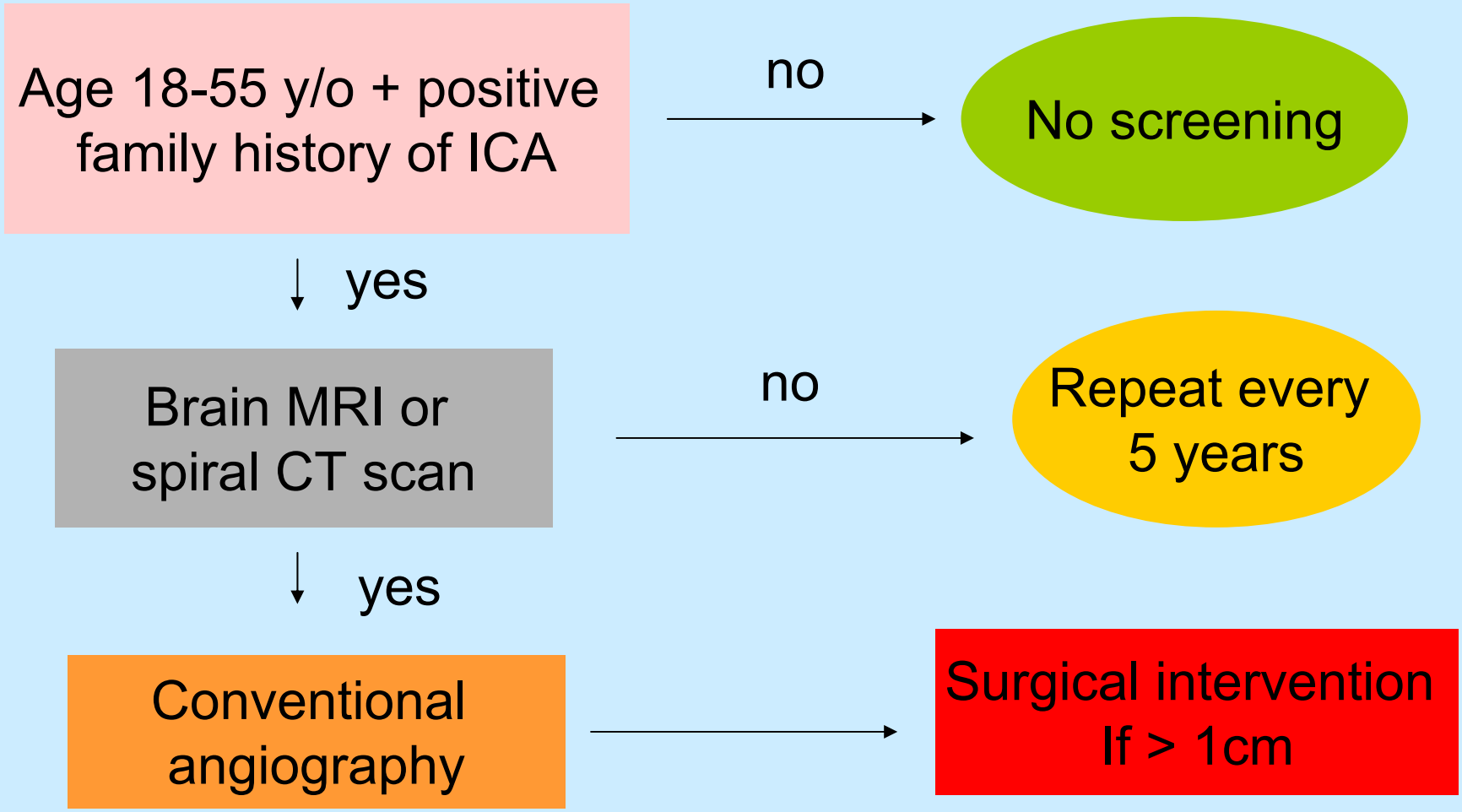
Neumann, Curr Opin nephrol Hyper, 11(5), 2002

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



Gibbs, KI, 65, 2004

表2-1. 台灣地區末期腎臟疾病病患之盛行率「年齡、性別、原發病因」

	88 年人口數	88 年透析病患數	百分比	盛行率 (人／每百萬人口)
年齡				
0~19 歲	6,674,848	232	0.86	35
20~44 歲	9,411,444	5,385	19.85	572
45~64 歲	4,140,623	12,012	44.28	2,901
65~74 歲	1,229,338	6,507	23.99	5,293
75+ 歲	636,134	2,989	11.02	4,699
Missing		18		
性別				
男性	11,312,728	12,827		
女性	10,779,659	14,315		
Missing		1		
平均年齡	57.5 ± 14.8			
男性	57.0 ± 15.3			
女性	58.1 ± 14.3			
原發病因				
CGN		11,433	42.12	
TIN		443	1.63	
Hypertension		1,406	5.18	
DM		6,022	22.19	
Gout		353	1.30	
Cystic Kidney Disease		435	1.60	…5th
Obstructive Uropathy		140	0.52	
Stone		295	1.09	
Unknown		6,616	24.37	
Total		27,143	100.0	1,241

*資料來源：八十八年度血液透析院所媒體申報資料

USRDS, 2002

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

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

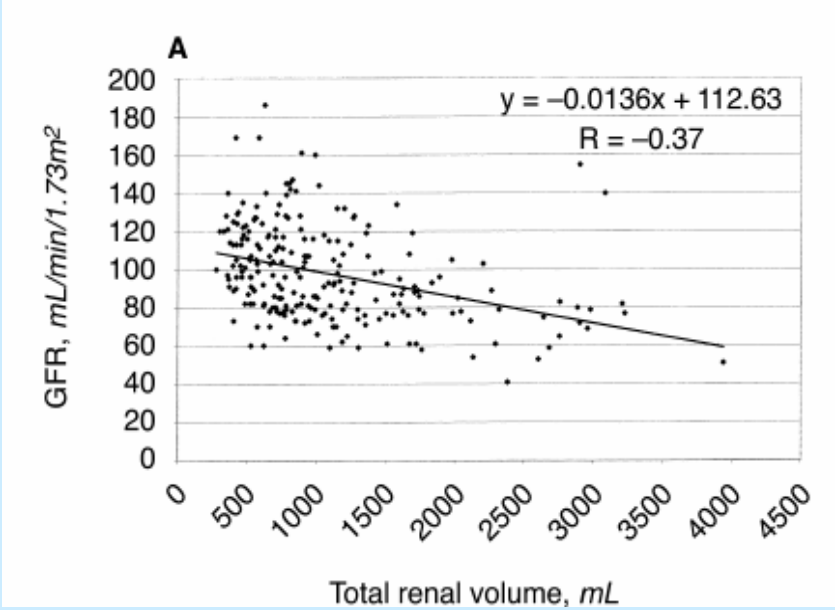
Fick-Brosnahan, AJKD, 39, 2002

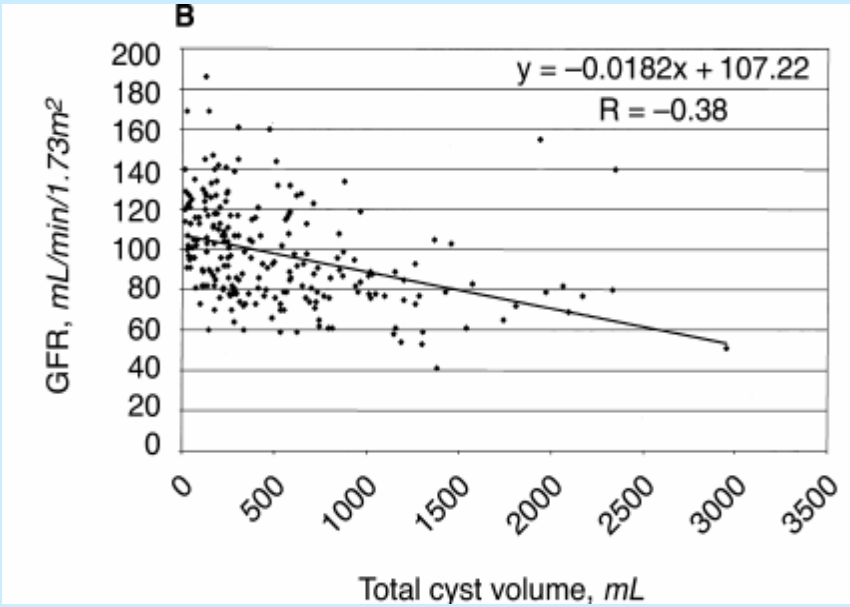
ADPKD and renal failure

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

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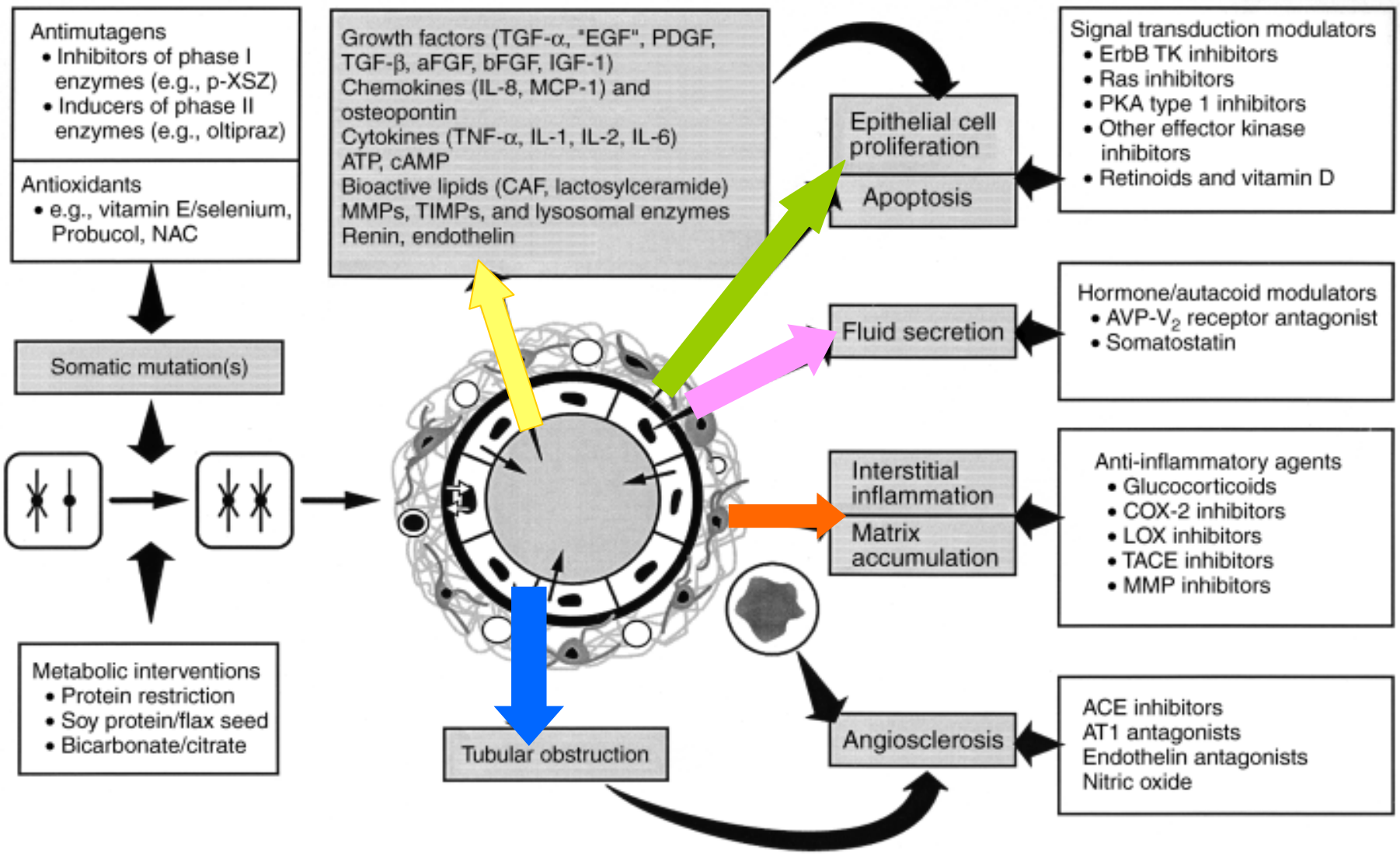
Treatment prospective



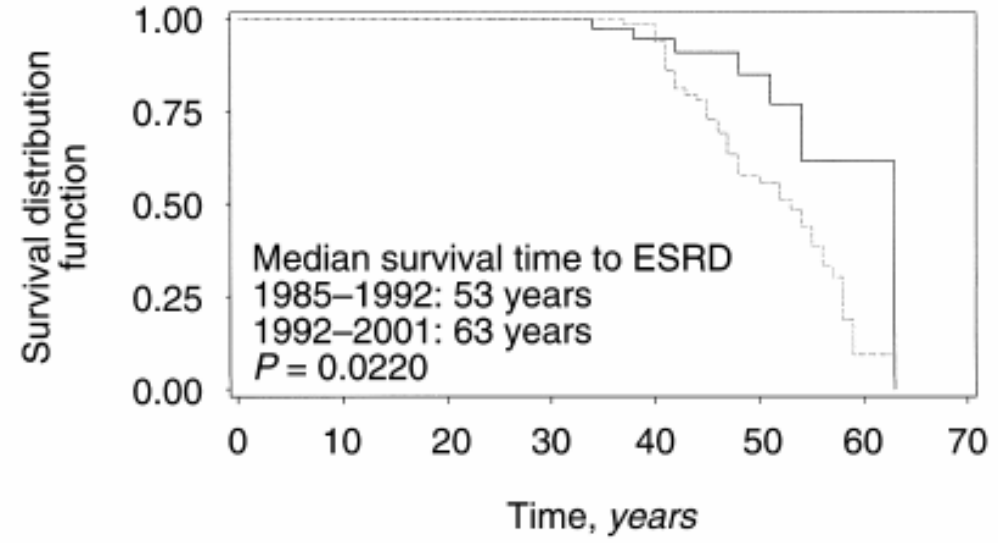
Qi Qian, KI, 63, 2001

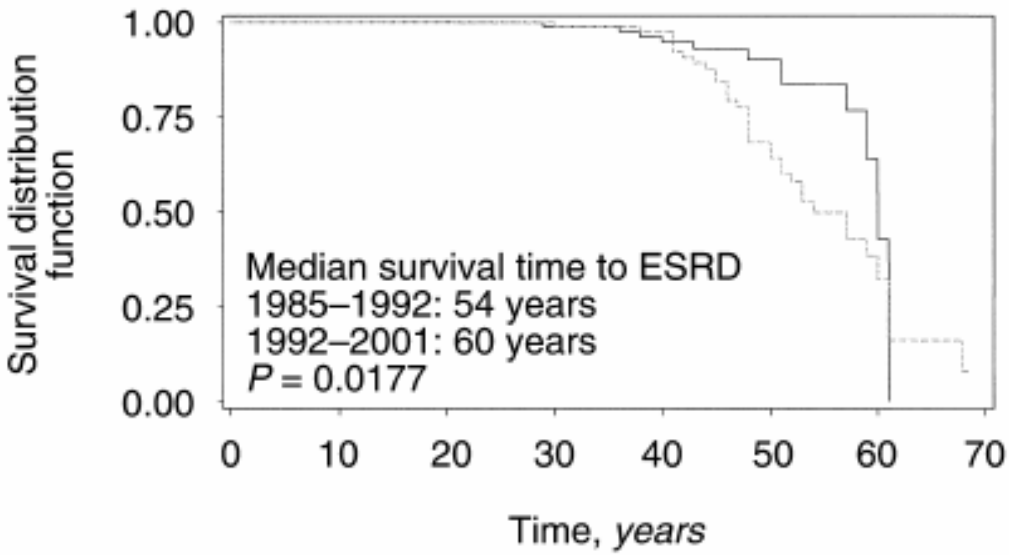
Treatment of HTN in ADPKD

- 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

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

van Dijk, NDT, 18, 2003

No effect of enalapril in hypertensive ADPKD patients

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

van Dijk, NDT, 18, 2003

Therapeutic strategies to retard progression

Treatment	Benefit
Antihypertensive agent	
Enalapril/losartan	yes?
ACEI	
± diuretics	no
± CCB	no
± other	no
Dietary manipulation	
Protein restriction	yes/no
Soy protein	yes
Fish oil	no
Flaxseed	yes

Treatment	Benefit
Lipid-lowering therapy	
Lovastatin	yes
Probucol	yes
α-tocopherol	no
Other	
Taxanes	yes/no
Potassium citrate	no
Sodium bicarbonate	no
Methylprednisolone	no

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** →

→ **Low dose opioids**

- Acetaminophen
- Salsalate
- NSAIDs
- Cox-2 inhibitor
- Tramadol
- Clonidine

→**Transcutaneous electrical nerve stimulation/acupuncture**

→**Spinal cord stimulation/ neuraxial opioids and local anesthetics**

→**Surgical approach (liver/kidney)** →
- Decompression
- Decortication
- Hepatectomy
- Renal denervation
- Nephrectomy

Bajwa, KI, 60 (5), 2001

@ Genetics

@ Cell biology and pathogenesis

@ Clinical picture

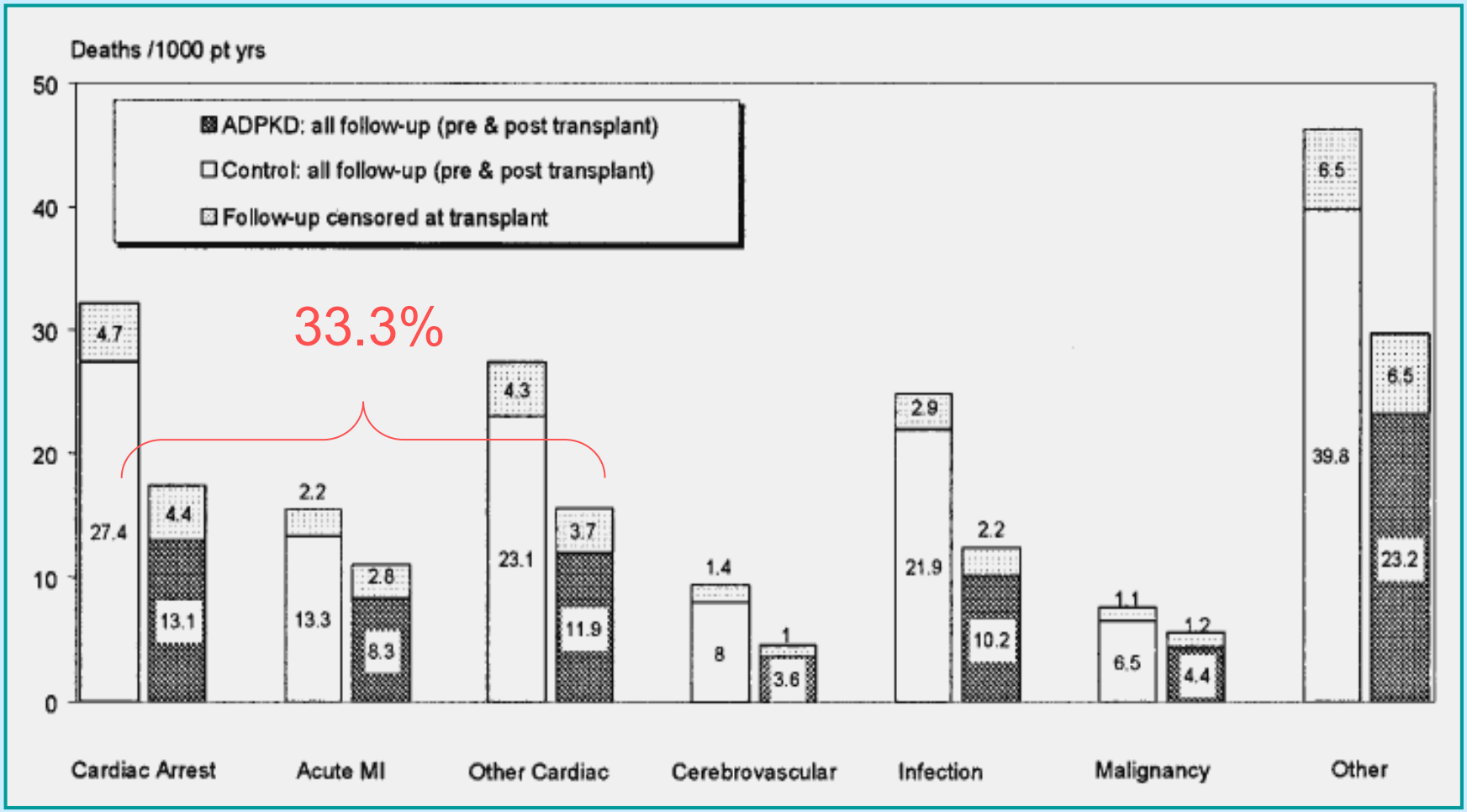
@ Complication

@Treatment prospects

@ Outcome

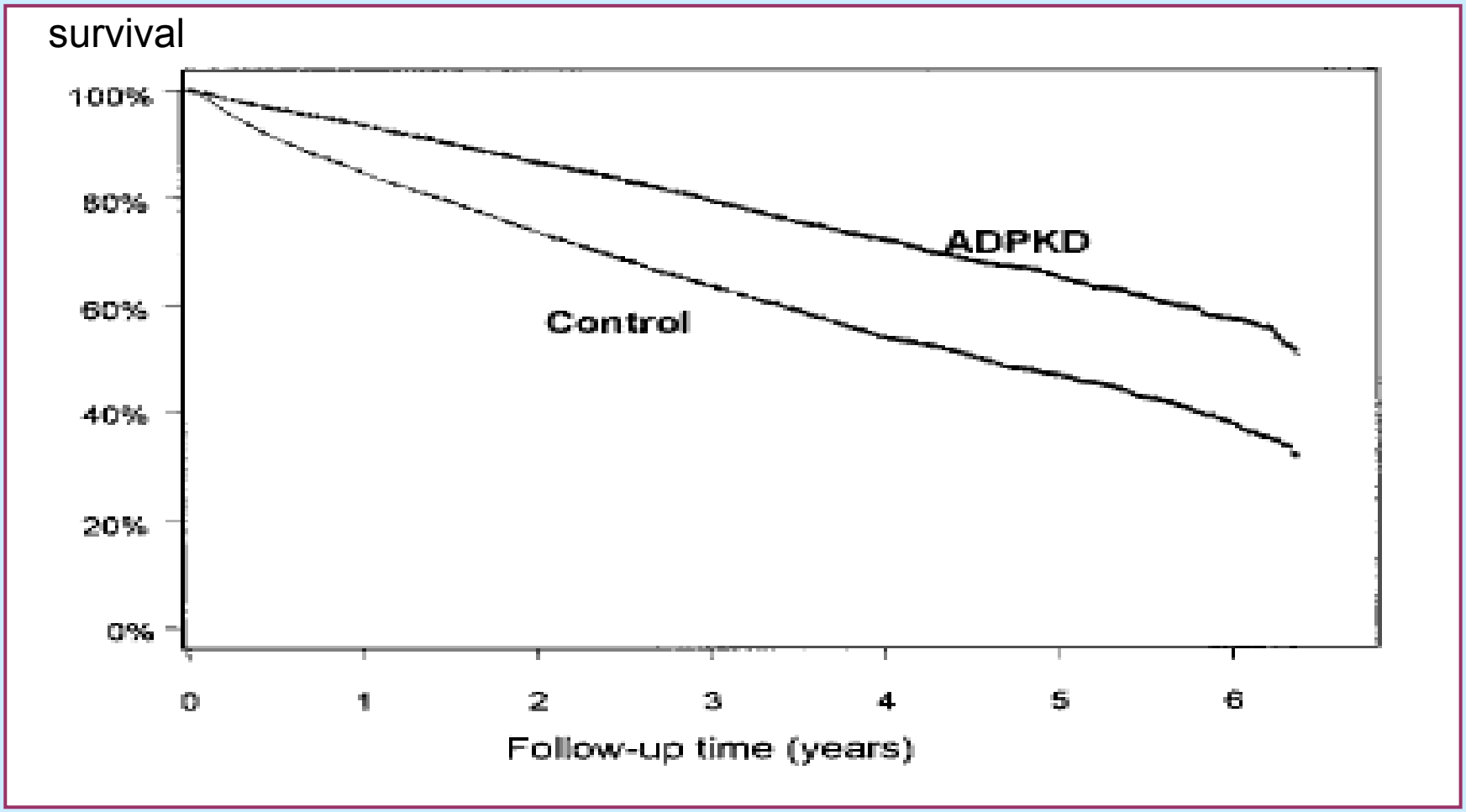
@ Screening & genetic counseling

Death in ADPKD



Perrone, AJKD, 38(4), 2001

Survival of ADPKD after ESRD



Perrone, AJKD, 38(4), 2001

Death from extrarenal manifestation

	No. Patients		No. Deaths per 1,000 Patient-Years		
	Control	ADPKD	Control	ADPKD	*P* Value
N	9,435	9,435			
Deaths from all causes	3,414	2,054	156	81	≤0.0001
Deaths from extrarenal manifestations					
Polycystic liver disease (item 68, HCFA 2746) or cirrhosis (item 67, HCFA 2746) or liver failure, cause unknown other (item 69, HCFA 2746)	62	38	3	2	≤0.0020
Polycystic liver disease (item 68, HCFA 2746)	0	20	0	1	≤0.0001
Cardiac valvular disease (item 30, HCFA 2746)	73	53	3	2	0.0067
Cerebrovascular disease including intracranial hemorrhage (item 36, HCFA 2746)	200	112	9	4	≤0.0001
Perforation of bowel (not peptic ulcer) (item 76, HCFA 2746) (diverticular disease)	23	25	1	1	0.7966
Hemorrhage from ruptured vascular aneurysm (item 41, HCFA 2746)	17	16	1	1	0.5417

Perrone, AJKD, 38(4), 2001

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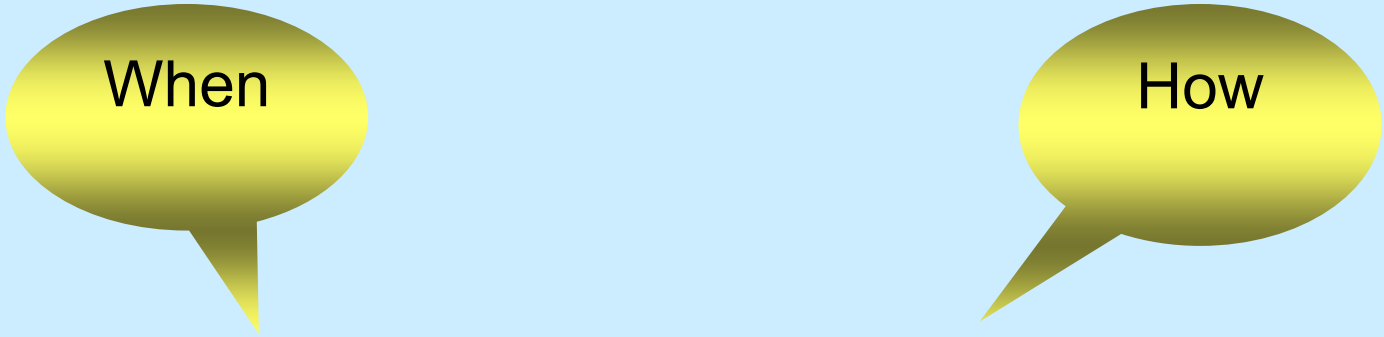
Each child of affected person has 50% chance to inheriting the disease gene !



Screening and Genetic counseling

Especial clinical conditions??

- Genetic counseling and medical ethics

- Antenatal screening:
  - Prenatal ultrasound: Renal cyst
    Oligohydramnio
  - 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!!!

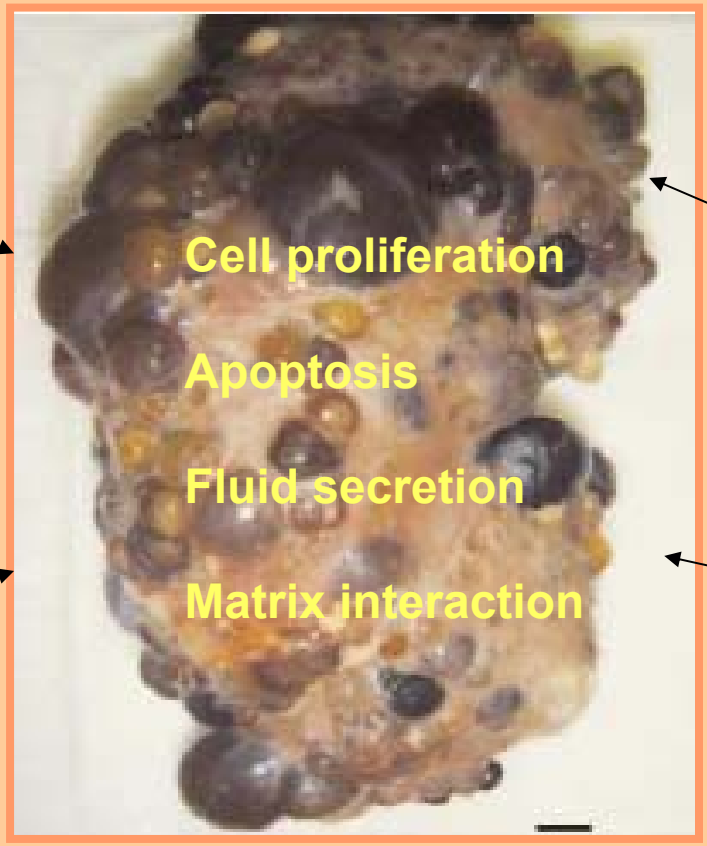
Cyst Initiation

Cyst enlargement

Germline mutations

- PKD1 gene
- PKD2 gene

Somatic mutations



Modifying genes

Environmental factors

- Family history
- Screening

Progression

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