Autosomal Dominant Polycystic Kidney

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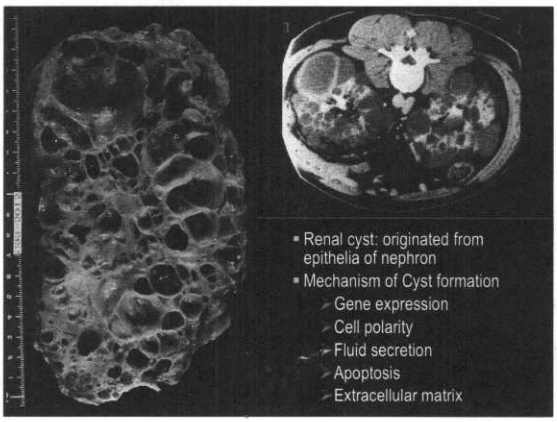


Epidemiology

- 3rd most frequent inherited monogenic disease
- The most common monogenic disorder that is potentially fatal
- Prevalence:
  - ◆ General population: 1/400 ~ 1/1,000(white)
    - ➢ x2 cystic fibrosis
    - ➢ x10 Huntington's ds
  - ◆ Maintenance dialysis: 2~10% (1.7% in Korea, 1998)
- Mean age at Dx: 43 (이중건, 96)
- Mean age at ESRD: 48 (이중건, 96)

Clinical Presentations

- Renal Manifestations
  - ◆ Microscopic hematuria
  - ◆ Proteinuria(18%)
  - ◆ Hypertension
  - ◆ Renal failure
  - ◆ Pain
  - ◆ Bleeding
  - ◆ Infection
  - ◆ Calculus
  - ◆ Cancer
- Extrarenal manifestations
  - ◆ Extrarenal cyst
    - ➢ Hepatic
    - ➢ Pancreas
    - ➢ Spleen
    - ➢ Ovary
  - ◆ Diverticulosis coli
  - ◆ Cardiac valvular disease
  - ◆ Intracranial aneurysms
  - ◆ Inguinal hernias

Renal Manifestations

Features	이중건(%)	황대연 (%)	Others (%)
▪ Hypertension >80% with hematuria, UTI, nephrolithiasis ± Renal failure			
▪ Progressive Kidney enlargement			
▪ Decreased urine-concentrating ability			
▪ Preserved erythropoietin production			
Hematuria(microscopic)	34	-	25

* Sx at initial presentation, ** @ 50yr, *** renal calcification

Extrarenal Manifestations

Features	이중건(%)	황대연 (%)	Others (%)
Headache	70		
Intracranial Aneurysms		8	7.9 - 10
Stroke	5.6		
Valaular heart ds	7/19*		39
MVP	0	0	30
Hepatomegaly	48		30
Hepatic cysts	76	82	75
Colonic diverticulum		13	70-80

* Among selected cases, ** @ 50yr

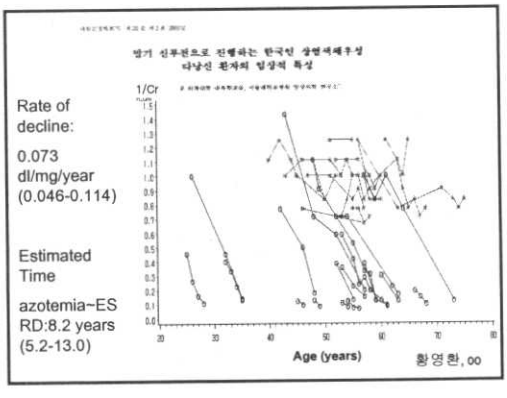
Diagnostic Cirtieria for ADPKD

- Primary critieria
  - ◆Innumerable fluid-filled cysts scattered diffusely throughout the renal cortex and medulla
  - ◆Definite history of PKD in genetically related family members
- Secondary critieria
  - ◆Polycystic liver, Renal insufficiency, Abdominal hernia, Cardiac valvular lesions, Pancreatic cysts, Cerebral aneurysm, Seminal vesicle cysts, Drooping eyelids
- A certain dx of ADPKD: 1st criteria only

Ravine's Critieria

- < 30 yrs: 2 cysts(bilateral or unilateral)
- 30-59yrs: 2 cysts in each kidney
- >60yrs: > 4 cysts in each kidney

- For PKD1 family only



Poor Prognostic Factors for ADPKD

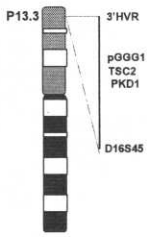
- PKD 1 family
- Young age at diagnosis, unless detected by screening
- African-american race(vs white: 43:55)
- Male
- Hypertension
- Gross hematuria
- Increased kidney size

Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 : PKD 2

PKD-1 Gene

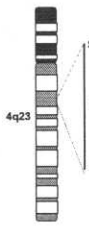
Chromosome 16



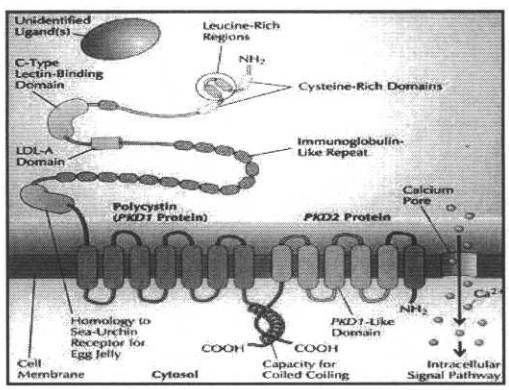
- 16p13.3
- genomic region 52 kb
- mRNA transcript 14,148 bp
- 46 exons
- 4,302 aas
- 460kd protein(polycystin 1)
- Exon 1-33: severalduplications in 16p(pseudogenes)
- HG loci: 16p13.1 >95%

PKD-2 Gene

Chromosome 4



- Locus : 4q21-23
- Gene length: 68 kb
- Exon number: 15
- mRNA transcript: 5.4Kb
- 25% homology to PKD1 gene



Examples of Locus Heterogenecity

Disease	Description	Chx Location
Retinitis pigmentosa	Progressive retinopathy & loss of vision	>20
Osteogenesis imperfecta	Brittle bone disease	7,17
Carcot-Marie-Tooth ds	Peripheral neuropathy	1,5,8,11,17,X
Familial Alzheimer ds	Progressive dementia	1,14,19,21
Familial melanoma	Autosomal dominant melanoma	1,9
Hereditary nonpolyposis colorectal cancer	Autosomal dominant colorectal cancer	2p,2q,3,7
Autosomal dominant breast cancer	Predisposition to early-onset breast and ovarian cancer	13,17
Tuberous sclerosis	Seizure, facial angiofibroma, hypopigmented macules, mental retardation	9,16
ADPKD	Accumulation of renal cysts	4,16

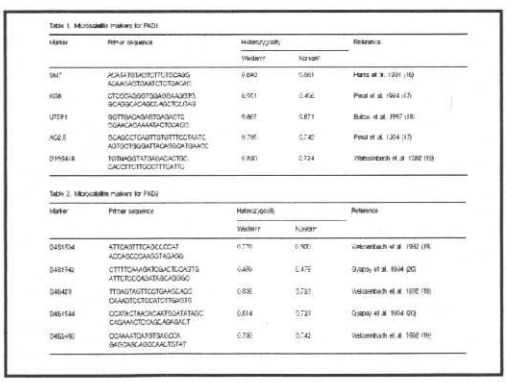
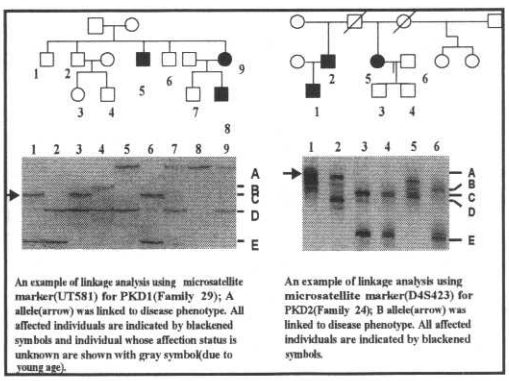


Table 1. Microsatellite markers for PKD1

Marker	Primer sequence	Heterozygosity		Reference
		Weber*	Kanton*	
SM7	ACAGATGTCACTCTTCTCCAGG AGAAGACTGAATCTCTGACAC	0.840	0.661	Hans et al. 1991 (16)
KG8	CTCCCAGGGTGGAGGAAGGTG GCAGGCACAGCCAGCTCCAG	0.951	0.456	Peral et al. 1994 (17)
UT581	GGTTGACAGAGTGAGATC CGAACACAAAGACTCCACC	0.867	0.671	Bulka et al. 1997 (18)
AG2.5	ACAGCCTCAGTTGTATTTCCTAATC ATTCTTGGAATTACAGGCATGAATC	0.795	0.742	Peral et al. 1994 (17)
D16S415	TGTAAGGTATGAGACACTTC CACCTTCTTGCCTTTGATTC	0.930	0.724	Watkombach et al. 1992 (19)

Table 2. Microsatellite markers for PKD2

Marker	Primer sequence	Heterozygosity		Reference
		Weber*	Kanton*	
D4S1534	ATTGAGTTTCAGCCCCAT ACCAGCCCAAGGTAGAGG	0.770	0.700	Watcombach et al. 1992 (19)
D4S1542	CTTTTCAAAGTGAGTCAGTG ATTCTCCCAGATAGCAGGGC	0.820	0.475	Gyapay et al. 1994 (20)
D4S423	TTGAGTAGTTCGTGAAGCAGC CAAGTCCTCCATCTTGATG	0.838	0.731	Watcombach et al. 1992 (19)
D4S1544	CCATACTAACACAATGGATATAGC CAGAAACTCCAGCAGAGACT	0.814	0.731	Gyapay et al. 1994 (20)
D4S2460	CCAAAATCAATGTGAGCCA GAGCAACAGCCAACTGTAT	0.790	0.742	Watcombach et al. 1992 (19)



An example of linkage analysis using microsatellite marker(UT581) for PKD1(Family 29); A allele(arrow) was linked to disease phenotype. All affected individuals are indicated by blackened symbols and individual whose affection status is unknown are shown with gray symbol(due to young age).

An example of linkage analysis using microsatellite marker(D4S423) for PKD2(Family 24); B allele(arrow) was linked to disease phenotype. All affected individuals are indicated by blackened symbols.

상염색체 우성 다낭신의 진단을 위한
Microsatellite Marker 개발

김현호 · 남궁환 · 김성주* · 안규리† · 김영란

Short Report

Genetic heterogeneity in Korean families with autosomal-dominant polycystic kidney disease (ADPKD): the first Asian report

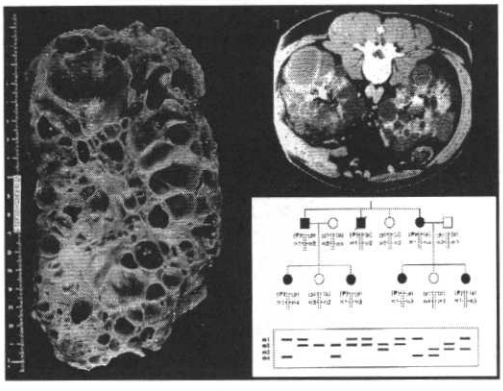
Jung Geon Lee*, Kyu Back Lee*, Un Kyung Kim†, Curie Ahn‡, Dae Yeon Hwang*, Young Hwan Hwang*, Hyun-Seon Eo*, Eun Joo Lee*, Yon Su Kim†, Jin Suk Han*, Sukgyeun Kim* and Jung Sang Lee*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease in adults, and the prevalence of the disease within the chronic haemodialysis patient popula-

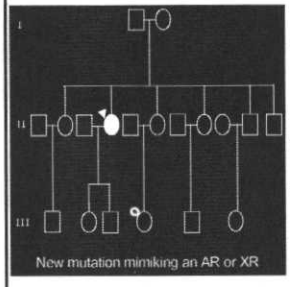
Table 4. Clinical findings according to linkage analysis results

Parameters	PKD1	PKD2	p-value
Total no.	126	24	
Age [median (range)]	41 (12–82)	52 (13–67)	0.309
Sex	61:65	15:9	0.237
Dx age [median (range)]	35 (12–68)	48 (13–58)	0.167
Hypertension (%)	49 71 (69)	12 22 (55)	0.304
Age [median (range)]	38 (25–57)	53 (36–59)	0.003
CVA (%)	17 126 (14)	2 22 (9)	0.496
Age [median (range)]	45 (32–60)	47, 53	0.823
Liver cysts (%)	30 47 (64)	3 5	1.000
Renal failure (%)	14 126 (11)	1 22 (5)	0.567
Age [median (range)]	48 (39–71)	67	0.520
Death	21	2	
Age [median (range)]	55 (40–70)	53, 79	0.229
Causes	CVA (7) Sudden death (3) Renal failure (1) TPL Cx (1) Accident (1) Unknown (8)	CVA (1) Unknown(1)	

Dx – diagnosis; CVA – cerebrovascular accident; TPL – transplantation; Cx – complication.



New mutation

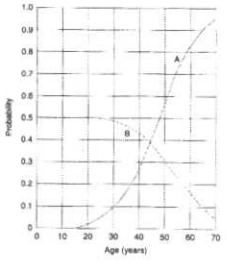


New mutation mimiking an AR or XR

- Single AD in a family
  - ❖7/8 of all cases of achondroplasia
  - ❖2-40% in ADPKD(av 25%)
- 10^5~ 10^6/locus/ gamate/generation
- Couple carried 2-3% risk for other anormalities as general populations

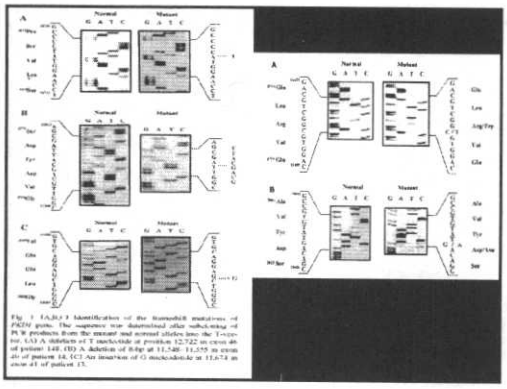
Late Onset

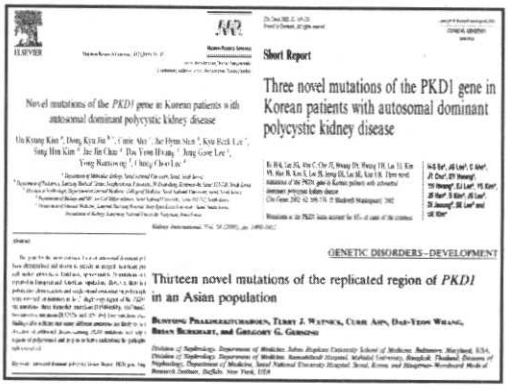
- Age onset curve for Huntington ds
- Age 10:→ 8%
- Age 30:→ 100%



Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 .. PKD 2
- Alleleic heterogeneity





Short Report

Three novel mutations of the PKD1 gene in Korean patients with autosomal dominant polycystic kidney disease

Novel mutations of the *PKD1* gene in Korean patients with autosomal dominant polycystic kidney disease

GENETIC DISORDERS–DEVELOPMENT

Thirteen novel mutations of the replicated region of *PKD1* in an Asian population

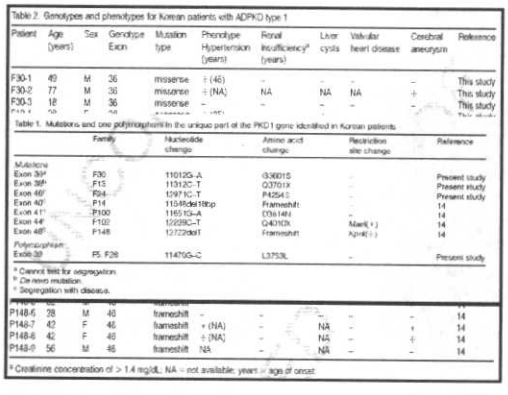


Table 2. Genotypes and phenotypes for Korean patients with ADPKD type 1

Patient	Age (years)	Sex	Genotype Exon	Mutation type	Phenotype Hypertension (years)	Renal insufficiency[a] (years)	Liver cysts	Valvular heart disease	Cerebral aneurysm	Reference
F30-1	49	M	36	missense	+ (46)	–	–	–	–	This study
F30-2	77	M	36	missense	+ (NA)	NA	NA	NA	+	This study
F30-3	18	M	36	missense	–	–	–	–	–	This study

Table 1. Mutations and one polymorphism in the unique part of the PKD1 gene identified in Korean patients

	Family	Nucleotide change	Amino acid change	Restriction site change	Reference
Mutations					
Exon 30[a]	F30	11012G-A	G3601S		Present study
Exon 39[b]	F15	11312C-T	Q3701X		Present study
Exon 46[c]	F24	12971C-T	P4264L		Present study
Exon 40[c]	P14	11848del18bp	Frameshift		14
Exon 41[c]	P100	11851G-A	G3951N	–	14
Exon 44[c]	F102	12269C-T	Q4010X	MaeII(+)	14
Exon 46[c]	P148	12722delT	Frameshift	XpnI(+)	14
Polymorphism					
Exon 39	F5, F28	11470G-C	L3753L	–	Present study

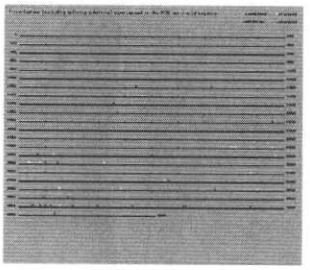
[a] Cannot test for segregation.
[b] De novo mutation.
[c] Segregation with disease.

P148-5	28	M	46	frameshift	–	–	–	–	14
P148-7	42	F	46	frameshift	+ (NA)	–	NA	+	14
P148-8	42	F	46	frameshift	+ (NA)	–	NA	+	14
P148-9	56	M	46	frameshift	NA	–	NA	–	14

[a] Creatinine concentration of > 1.4 mg/dL. NA = not available; years = age of onset.

Mutations of PKD-1

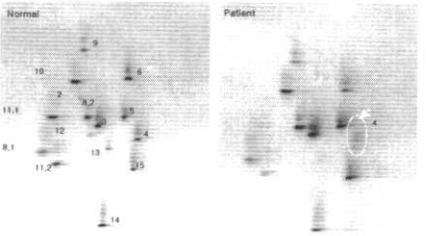
- 3'-Single copy region
- Ca 50 mutations
  - ◆non-sense mutation
  - ◆small deletion
  - ◆frameshift mutation
- No hot spots



Mutation Detection

- Mutations throughout gene without hot spot
- PKD1 gene
  - ◆Mutation detection in duplicated region
    - ➢DHPLC with long-range PCR
    - ➢Protein truncation test
  - ◆Earlier renal failure gene: in 5' ends(Rossetti, 2002, JASN)
- PKD2 gene
  - ◆Truncated mutation(95%)
  - ◆No relationship between the location of mutations and clinical severity

TDGS(Two-Dimensional Gene Scanning)

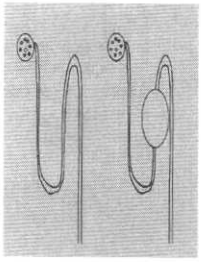


DNA fragments are separated by melting point of DNA fragments on Urea-Formamide gradient gel

Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 .. PKD 2
- Alleleic heterogeneity
- Intra-familial variable expression

Segmental Involvement



- Only 1-5% of the nephrons make cysts
- Inherited susceptability + a subsequent so-called activating event

ADPKD is a Focal Disease

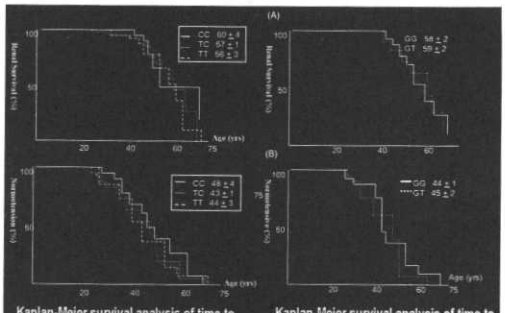
- Involve a small fraction of renal tubular cells
- Two hit model of cytonenesis
  - ◆Second somatic mutation is mandatory
  - ◆Loss of wild type allele
- Dominant inheritance, But molecular recessive mechanism
- Relatively high rate of somatic mutation in the kidney

Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 : PKD 2
- Alleleic heterogeneity
- Intra-familial diversity
  - ◆Stability of DNA→ susceptibility to the second hit

Effect of Modifying Gene in ADPKD

- TGFβ
  - ◆Expression: in all cell types of glomerulus & proximal tubule
  - ◆Reduce degradation of ECM
  - ◆Contribute to matrix accumulation
  - ◆Roles in DMN & GN
    - Renal fibroblast
      - ➢ Cell proliferation
      - ➢ Collagen production
- ecNOS
  - ◆Endothelial Constitutive Nitirc Oxide Synthease
  - ◆Endothelial NO by ecNOS
  - ◆Fx
    - ➢ Vasodilation
    - ➢ Anti-thrombotic effects
    - ➢ Regulation of glomerular microcirculation
    - ➢ Renal functional reserve
  - ◆Gene: Chx 7q35-36(26 exons)
  - ◆Exon 7 polymorphysm
    - ➢ Coronary artery spasm in Jpn



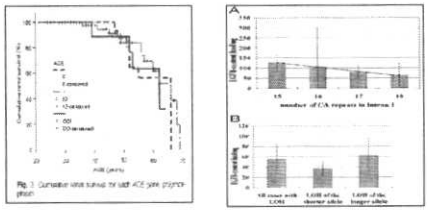
Kaplan-Meier survival analysis of time to the onset of (A) azotemia and (B) hypertension according to TGF-β1 T869C genotypes.

Kaplan-Meier survival analysis of time to the onset of (A) azotemia and (B) hypertension according to ecNOS Glu298Asp genotypes.

Effect of Modifying Gene in ADPKD

- EGFR
  - ◆EGF & cAMP: inc. the growth of cysts by stimulating cellular proliferation & fluid secretion
  - ◆Cystic hyperplasia
  - ◆EGFR
- ACE
  - ◆I/ / D polymorphism: DD has highest ACE level
  - ◆Related to hypertension
  - ◆Enhanced progression in renal disease(DD)
    - ➢IgAN
    - ➢FSGS

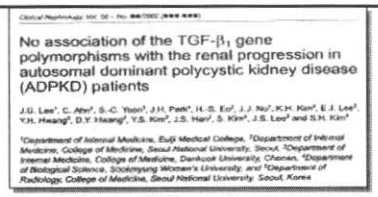
ACE **EGFR**



ACE gene polymorphism

Related to the development of ESRD in patients with diabetic nephropathy and IgA nephropathy (controvery)

Fig. 2. A graphical illustration of the influence of the smaller CA repeat allele on EGFR expression. The number of CA repeats in intron 1 is indicated on the X axis, the expression of EGFR on the Y axis (fmol/mg). Mean values with the corresponding standard deviations (bars) are indicated. B. Illustration of the influence of LOH on EGFR expression with a defined example of a 16/20 CA repeat allele composition. Columns represent the median; points and vertical lines represent mean values and the corresponding standard deviations.



No association of the TGF-β_1 gene polymorphisms with the renal progression in autosomal dominant polycystic kidney disease (ADPKD) patients

J.G. Lee[1], C. Ahn[2], S.-C. Yoon[3], J.H. Park[4], H.-S. Eo[2], J.J. No[2], K.H. Kim[2], E.J. Lee[3], Y.H. Hwang[2], D.Y. Hwang[2], Y.S. Kim[2], J.S. Han[2], S. Kim[3], J.S. Lee[3] and S.H. Kim[5]

[1]Department of Internal Medicine, Eulji Medical College, [2]Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, [3]Department of Internal Medicine, College of Medicine, Dankook University, Cheonan, [4]Department of Biological Science, Sookmyung Women's University, and [5]Department of Radiology, College of Medicine, Seoul National University, Seoul, Korea

The Korean J Genetics 24(3): 241-246, 2002

Title: The Glu/Asp Polymorphism of ecNOS Gene and the Renal Progression in Korean Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients

Jung Geon Lee[1], Curie Ahn[2], Sung-Chul Yoon[3], Jong Hoon Park[4], Jin Ju No[2], Chang Suk Moon[2], Eun Kyeung Song[2], Yeong Hwan Hwang[2], Dae Yeon Hwang[2], Yon Su Kim[2], Jin Suk Han[2], Suhnggwon Kim[2], Jung Sang Lee[2] and Seung Hyup Kim[5]

Variable Expression in ADPKD

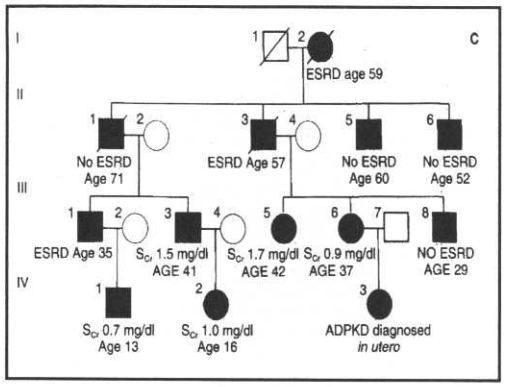
- Locus Heterogeneity: PKD 1 : PKD 2
- Alleleic heterogeneity
- Intra-familial diversity
  - ◆Stability of DNA→ susceptibility to the second hit
  - ◆Modifying gene
    - ➢ACE gene, CF gene?
      - Age onset of hypertension(DD 39.1, DI+II 42.6, 황대연등 1999)
    - ➢Not w TGFβ, ecNOS, EGFR

Anticipation and Repeat Extension

- More recent generation of a pedigree → earlier age of onset and/or more severe expression
- No of triple repeats is strongly correlated with severity of the disease(ex)
  - ◆5-30 copies no sx
  - ◆50 - 100 copies no sx or mildly affected
  - ◆100 - 1000 copies severe sx
- The number of repeats often increases with succeeding generations

Is there evidence for anticipation?

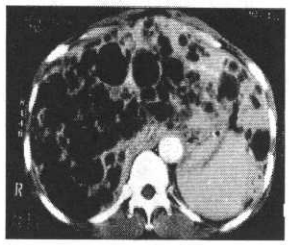
- Fick GM, Johnson AM, Gabow PA
  - ◆*Kid Int, 1994, 45(4):1153-62*
- Gonzalo A, Gallego A, San Millan JL, Ortuno J
  - ◆*Nephrol Dial Transplant 1996, suppl 6:21-3*
- Sotirakopolus N, Tsitios T, Stambolidow M,
  - ◆*Ren Fail 2001, 23(5):715-20*
- Cristodoulidou C, Spaia S, Mavromatidis K
  - ◆*Nephrol Dial Transplant 1995, 10(9):1603-6*



Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 : PKD 2
- Alleleic heterogeneity
- Intra-familial diversity
  - ◆Stability of DNA→ susceptibility to the second hit
  - ◆Modifying gene: ACE gene
    - ➢Not w TGFβ, ecNOS, EGFR
  - ◆Dynamic mutation: Anticipation

Hepatic cyst in ADPKD

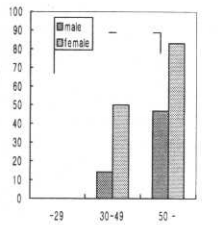


Liver Involvement

- Prevalence
- Mechanism
  - ◆Cystic dilation of biliary microhamartoma(hyperplastic embryonic intrahepatic bile duct origin)
- Clinical Features
  - ◆Compression: nausea, early satiety, supine dyspnea
  - ◆Obstruction: bile duct(jaundice), portal vein(portal hypertension), intrahepatic vena cava(ascites, edema)
  - ◆Hemorrhage, rupture, infection

Prevalence of Hepatic Cysts in Korea

Total: 116/148 (78.4%)
Male: 43/60 (71.7%)
Female: 73/88 (83.0%)

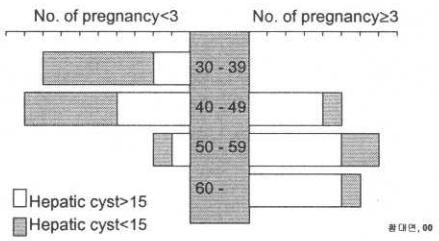


Clinical Manifestations

Symptoms & signs	Male	Female	%
Asymptom*	72.4	40.0	51.2
Abdominal fullness	13.8	25.0	19.0
RUQ discomfort*	10.3	40.0	29.8
Nausea/early satiety*	6.9	36.4	25.0
Chest tightness*	0.3	13.0	8.3
Other symptoms			9.5
Palpable liver mass	20.7	42.9	34.5
Tenderness on liver	3.4	26.8	16.7

*p<0.05

Hepatic cysts and No. of Pregnancy

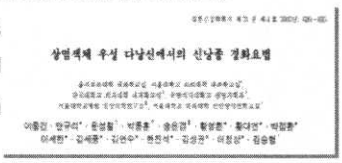


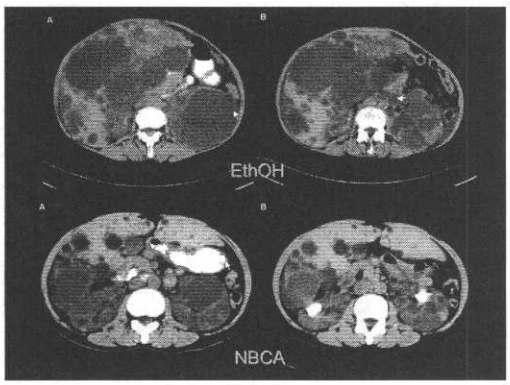
Variable Expression in ADPKD

- Locus Heterogeneity: PKD 1 .. PKD 2
- Alleleic heterogeneity
- Intra-familial diversity
  - ◆Stability of DNA→ susceptibility to the second hit
  - ◆Modifying gene: ACE gene
    - ➢Not w TGFβ, ecNOS, EGFR
  - ◆Dynamic mutation: Anticipation
  - ◆Environmental factors:
    - ➢female hormone for hepatic cyst
    - ➢Hypertension for renal failure

Treatment: *early treatment*

- **Dietary protein restriction: rodents(early)**
- **ACEI: Mashicho et al: no effect**
- **Hypertension control: ? no effect**
- **Lovast**
- **Steroid**
- **'Exorc)**


상염색체 우성 다낭신에서의 신낭종 경화요법

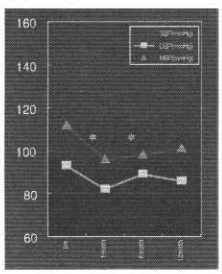


Sclerotherapy

- Ethanol
  - ◆Pigtail catheter
  - ◆Aspiration
  - ◆Filling out rh EthOH for 15-30min
  - ◆Needs admission
  - ◆Takes 3-5days
  - ◆Size>5cm
- NBCA-Lipiodol
  - ◆N-butyl cyanoacrylate
  - ◆Glue widely used in neuroradiologic intervention such as arteriovenous malformation for embolization
  - ◆NBCA-lipiodol mix→ slow injection after aspiration
  - ◆Same day, outpatient based procedure
  - ◆Multiple cysts intervention
  - ◆Size<5cm diameter

Effect of Sclerotherapy

- Patients
  - ◆1998.5 –2002.2
  - ◆24 patients
- Pain: 12/14
- Abdominal fullness 7/7
- Large cyst causing compression(>6cm): 3/3

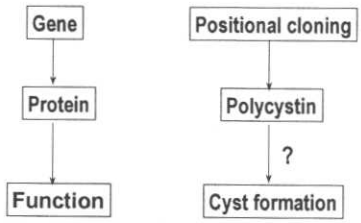


Decreased Arterial Blood Pressure After Procedure

Treatment Prospect for ADPKD

- From pathogenesis to treatment stratagies
  - ◆Antimutagens & antioxidants
  - ◆Dietary & metabolic interventions
  - ◆ErbB receptor & tyrosine kinase inhibitors
  - ◆cAMP antagonists & protein kinase A type I inhibitors
  - ◆Hormonal modulators
  - ◆Anti-inflammatory agents

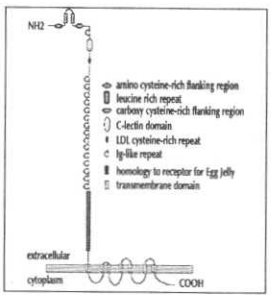
Pathogenesis



Lessons from Mouse Models

- Orthologues of human PKD genes : *Pkd1* & *Pkd2*
- Knockout mice lacking each gene – created
  homozygote – embryonic lethal
  heterozygote – develop cysts late in life
- Support two-hit hypothesis
- Trans-heterozygous mutations of *Pkd1* & *Pkd2* - more severe renal disease
  haploinsufficiency may play a role

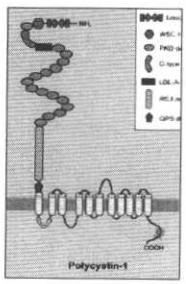
Polycystin 1



- 4,302-aa
- integral membrane glycoprotein
- 11 membrane spans
- ~2,500 aminoacid extracellular domain

Polycystin 1

- Large extracellular aa domain
  - ◆Many motifs
  - ◆Prot-prot interaction
  - ◆Prot-CHO interactions
  - ◆Receptor function?
- Cytoplasmic carboxyl terminus
  - ◆Potential site of phosphorylation



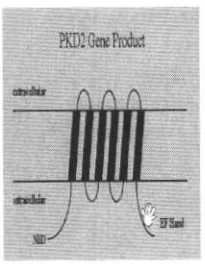
Polycystin I Expression

- Sites:
  - ◆renal tubular epithelia, hepatic bile ductules, pancreatic ducts, all sites of cyst formation in ADPKD
  - ◆brain, heart, bone, muscle
- Less abundant in adult than fetal epithelia
- In mature tubules – lateral membrane (site of cell-cell interaction)
- Over-expressed in most but not all cysts in kidneys from patients with ADPKD

Polycystin I: Function

- Unkown
- Adhesive protein-protein interactions
  - ◆Cell-cell interaction
  - ◆Cell-matrix interaction
  - ◆Protein-protein or protein-CHO binding
- Activate a number of intracellualr signaling pathways: Wnt, G-protein signaling
- Activate JAK-STAT signalling
  → Inhibit Cdk2(cyclin dependent kinase 2)

Polycystin 2



- 968 amino acid integral membrane protein
- 110 kd
- 6 transmembrane-spanning domains
- intracellualr N- and C- terminal tail
- Exon 12 coil structure: Ca binding EF -hand domain
- Exon 12-13: interacting w polycystin 1

Polycystin 2 : Expressions

- Distal tubule, collecting duct, thick ascending limb in normal fetal and adult kidneys
- Located @ ER
- Strong expression was noted in some, but not all, cysts form PKD1 & PKD2 cysts

Polycystin 2: Function

- Cell calcium signaling; iron channel
- Interact with polycystin I via their carboxy terminal coiled domains → create calcium-ermeable non-selective cation current

Pathogeneic Mechanisms of ADPKD

- Alterations in extracellular matrix
- Abnormal regulation of renal epithelial cell growth
  - ◆Overexpression of oncogenes:
    c-myc, c-fos, c-ha-ras, c-ki-ras
  - ◆bcl-2 overexpression
  - ◆Growth Factors: HGF, KGF, TGFα EGFR
- Abnormal fluid and electrolyte transport
  - ◆Related to adenyl cyclase signal transduction
  - ◆Cystic fibrosis transmembrane receptor(CFTR)를 통한 Cl-secretion

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