Human Genetics of Urinary Tract Malformation

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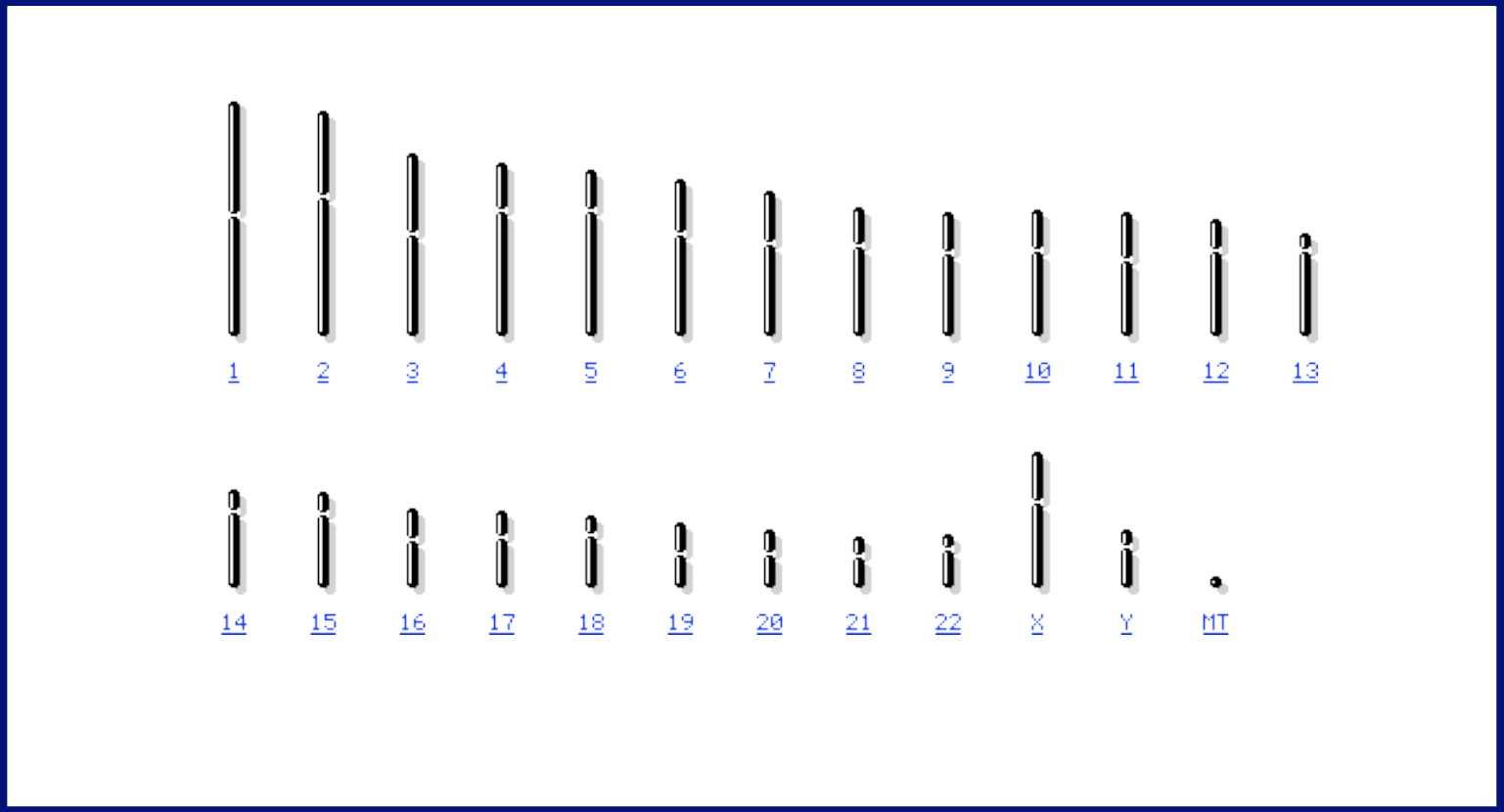

- The human genome is arranged in 23 pairs of chromosomes

- Contains 3 billion nucleotides

- Codes for ~25,000 genes

NCBI NCBI Map Viewer

PubMed | Entrez | BLAST | OMIM | Taxonomy | Structure

Search [ ] Find | Find in This View | Advanced Search

Homo sapiens (human) Build 36.2 (Current) BLAST The Human Genome

Chromosome: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 [**16**] 17 18 19 20 21 22 X Y MT

Query: **PKD1 or UMOD or BBS2 or SALL1** [clear]

Master Map: OMIM Morbid Summary of Maps Maps & Options

Region Displayed: **16pter-16qter**

Human genome overview page (Build 36.2)
Human genome overview page (Build 35.1)
Map Viewer Home
Map Viewer Help
Human Maps Help
FTP
Data As Table View
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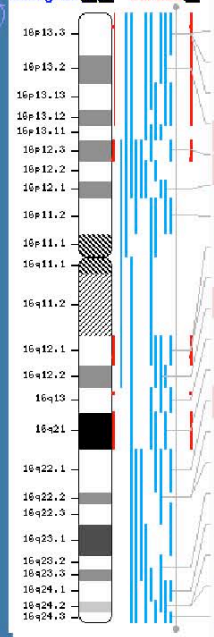
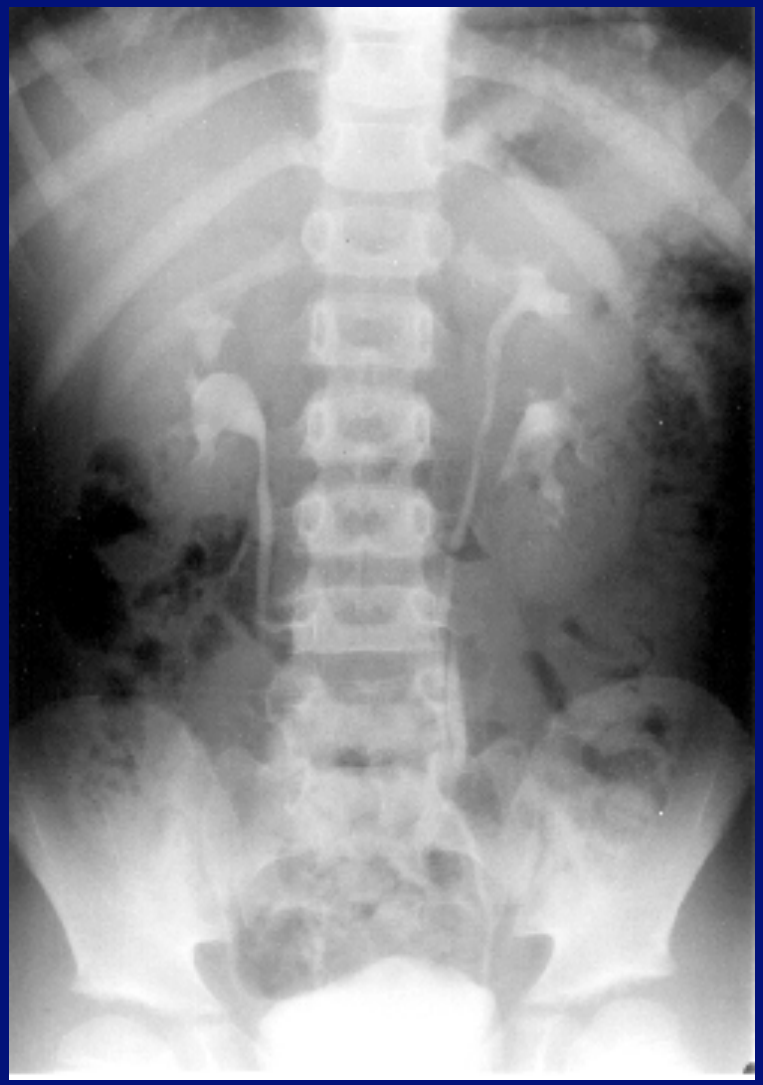


MIM Number	Symbol	GeneID	Disease
156850	MCOPCT1	8130	Cataract, congenital, with microphthalmia
601489	IGFALS	3483	Acid-labile subunit, deficiency of
137150	ABAT	18	GABA-transaminase deficiency
601313	PKD1	5310	Polycystic kidney disease, adult type I, 173900
191845	UMOD	7369	Hyperuricemic nephropathy, familial juvenile, 162000; Medullary cystic kidney disease 2, 603860; Glomerulocystic kidney disease with hyperuricemia and isosthenuria, 609886
172471	PHKG2	5261	Glycogenosis, hepatic, autosomal
107265	CD19	930	Antibody deficiency due to defect in CD19
607040	ABCC11	85320	Earwax, wet/dry, 117800
602218	SALL1	6299	Townes-Brocks syndrome, 107480; Townes-Brocks branchiootorenal-like syndrome, 107480
605018	CYLD1	1540	Cylindromatosis, familial, 132700
604110	GPR56	9289	Polymicrogyria, bilateral frontoparietal, 606854
606151	BBS2	583	Bardet-Biedl syndrome 2, 209900
114021	CDH3	1001	Hypotrichosis, congential, with juvenile macular dystrophy, 601553
218030	HSD11B2	3291	Apparent mineralocorticoid excess, hypertension due to; Hypertension, mild low-renin
276600	TAT	6898	Tyrosinemia, type II
609218	FHASD	550626	Foveal hypoplasia and anterior segment dysgenesis
605379	GAN	8139	Giant axonal neuropathy-1, 256850
608508	CYBA	1535	Chronic granulomatous disease, autosomal, due to deficiency of CYBA, 233690
606761	MLYCD	23417	Malonyl-CoA decarboxylase deficiency, 248360
155555	MC1R	4157	UV-induced skin damage, susceptibility to; Red hair/fair skin; Analgesia from kappa-opioid receptor agonist, female-specific; Oculocutaneous albinism, type II, modifier of

Summary of Maps:

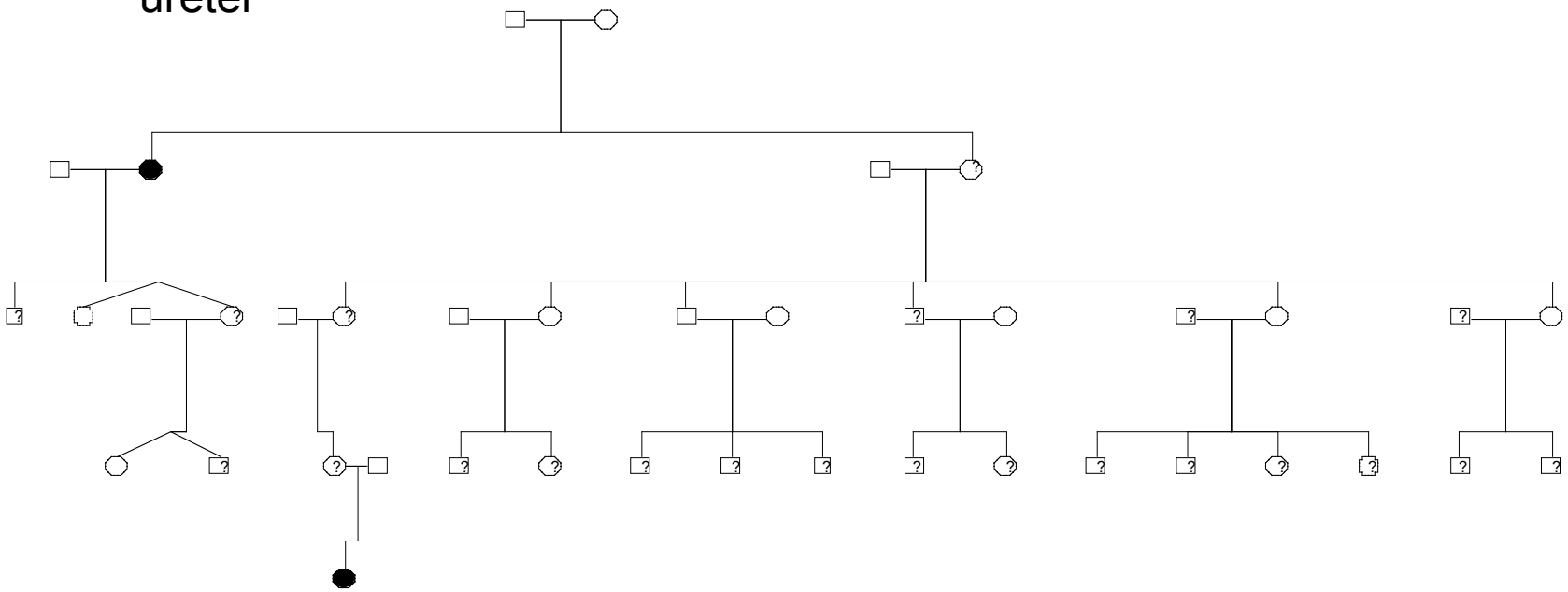
Map 1: Ideogram
Region Displayed: **16pter-16qter**
Map 2: OMIM Morbid Table View
Region Displayed: **16pter-16qter**
Total Markers On Chromosome: **109**
Markers Labeled: **20** Total Markers in Region: **109**

Case Presentation

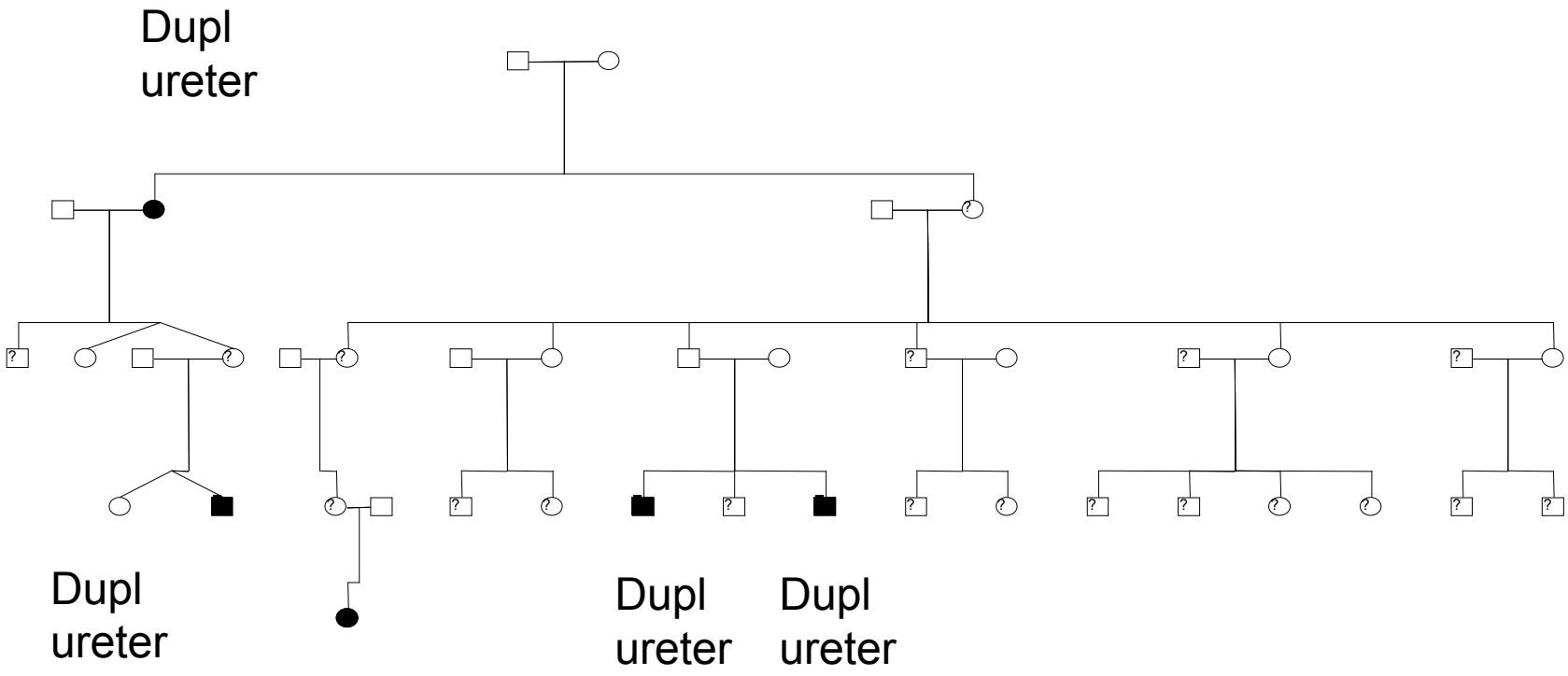


- 65 yo admitted fro acuter renal failure and sepsis
- History of renal stones
- Duplicated collecting system by ultrasound and CT scan.

Dupl
ureter

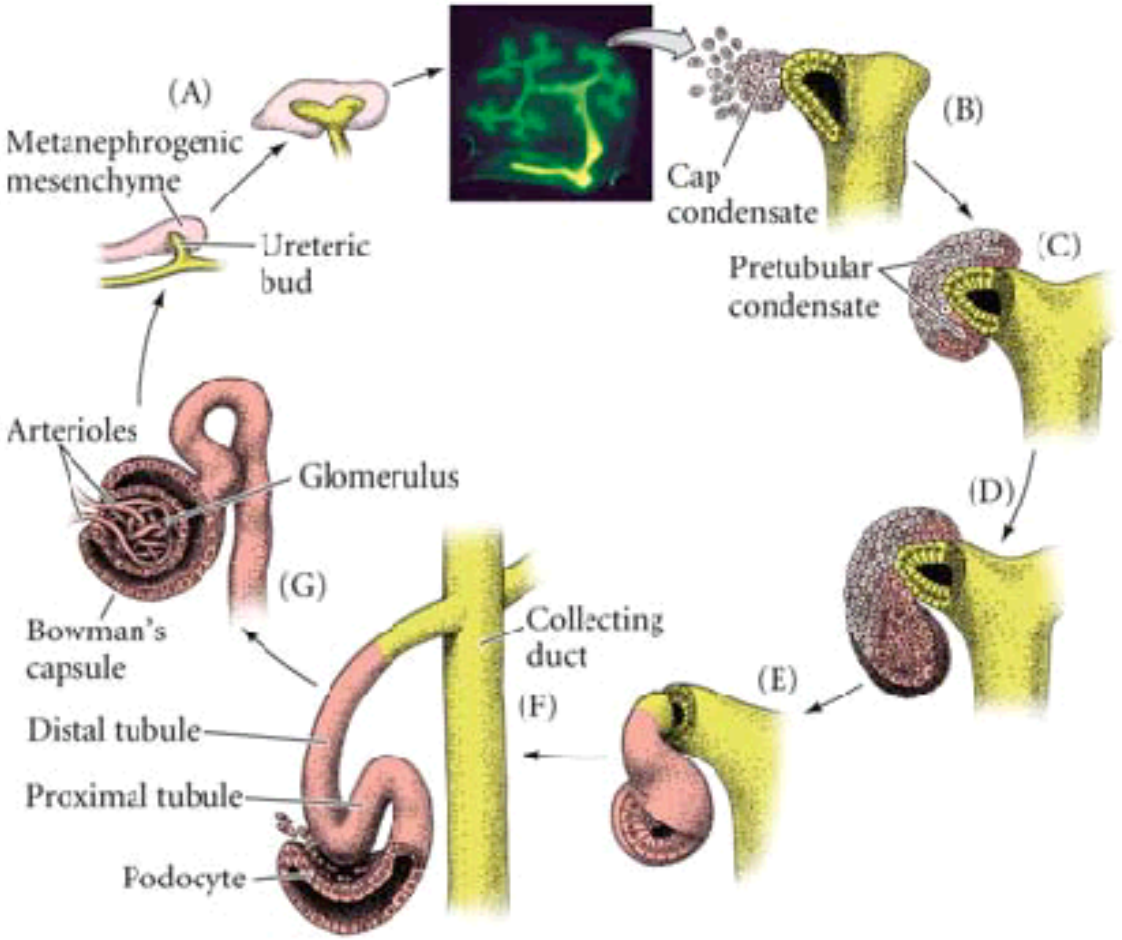


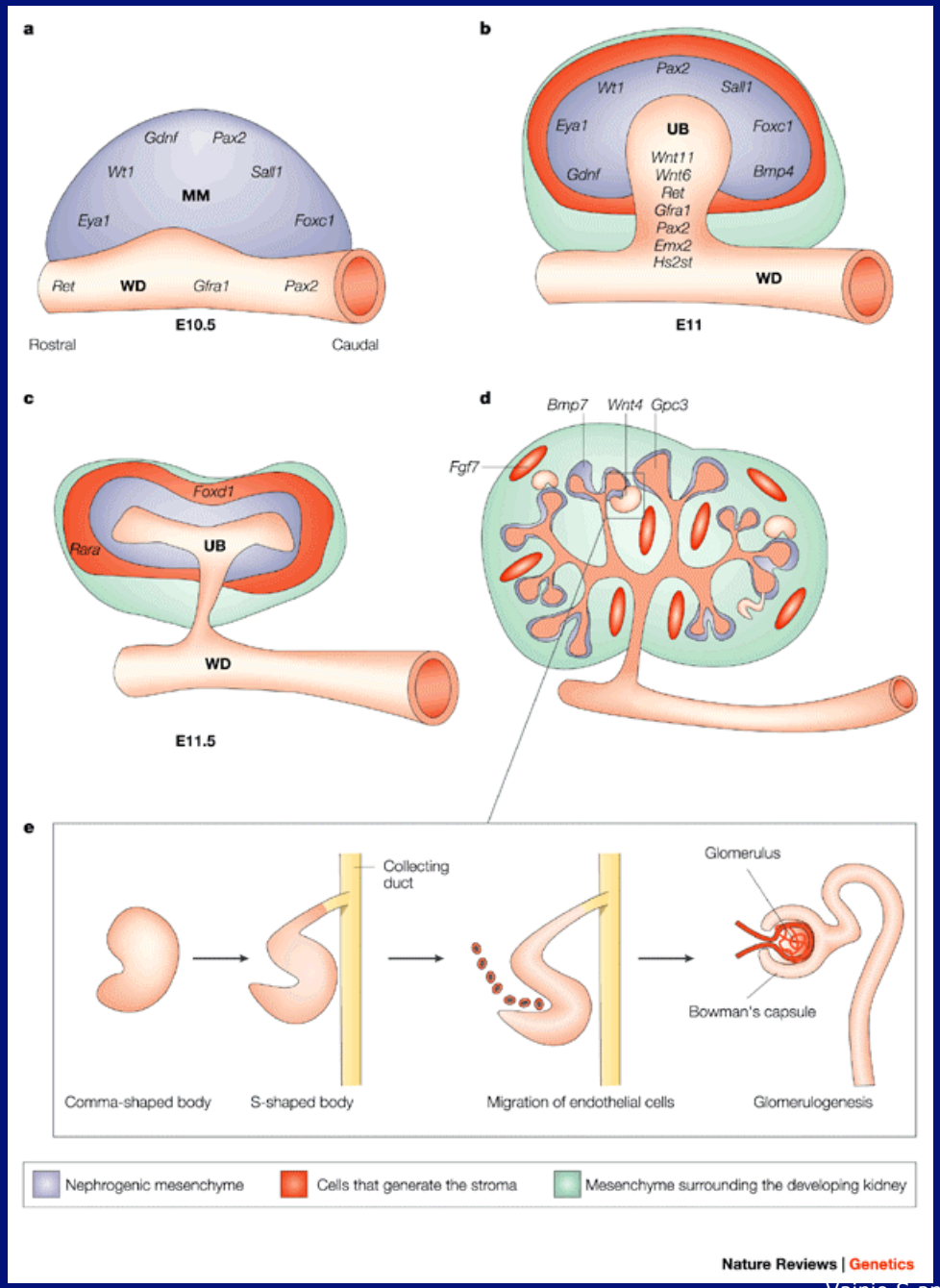
Kidney
Problem?

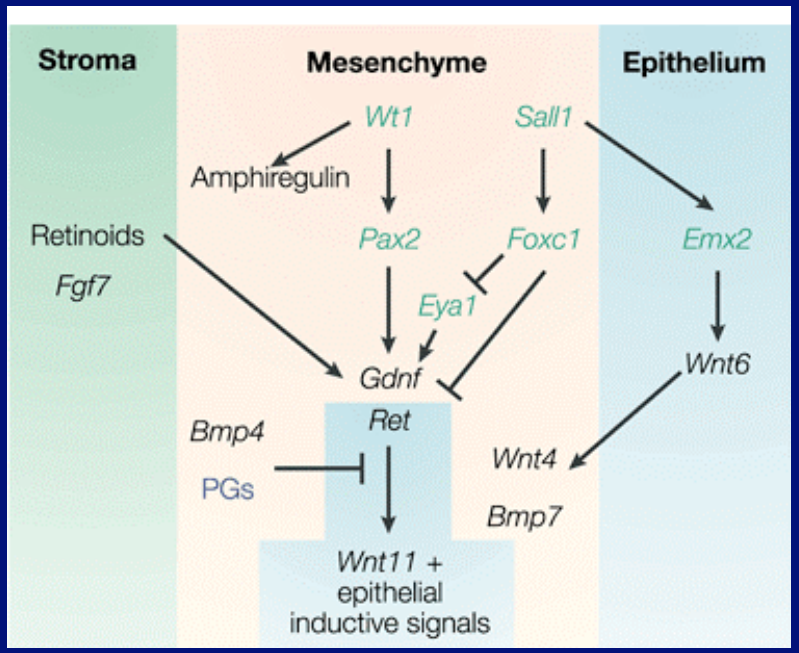

Dupl
ureter
Dupl
ureter
Dupl
ureter
Dupl
ureter
UPJ obstruction
Dupl ureter

Mammalian Kidney Development

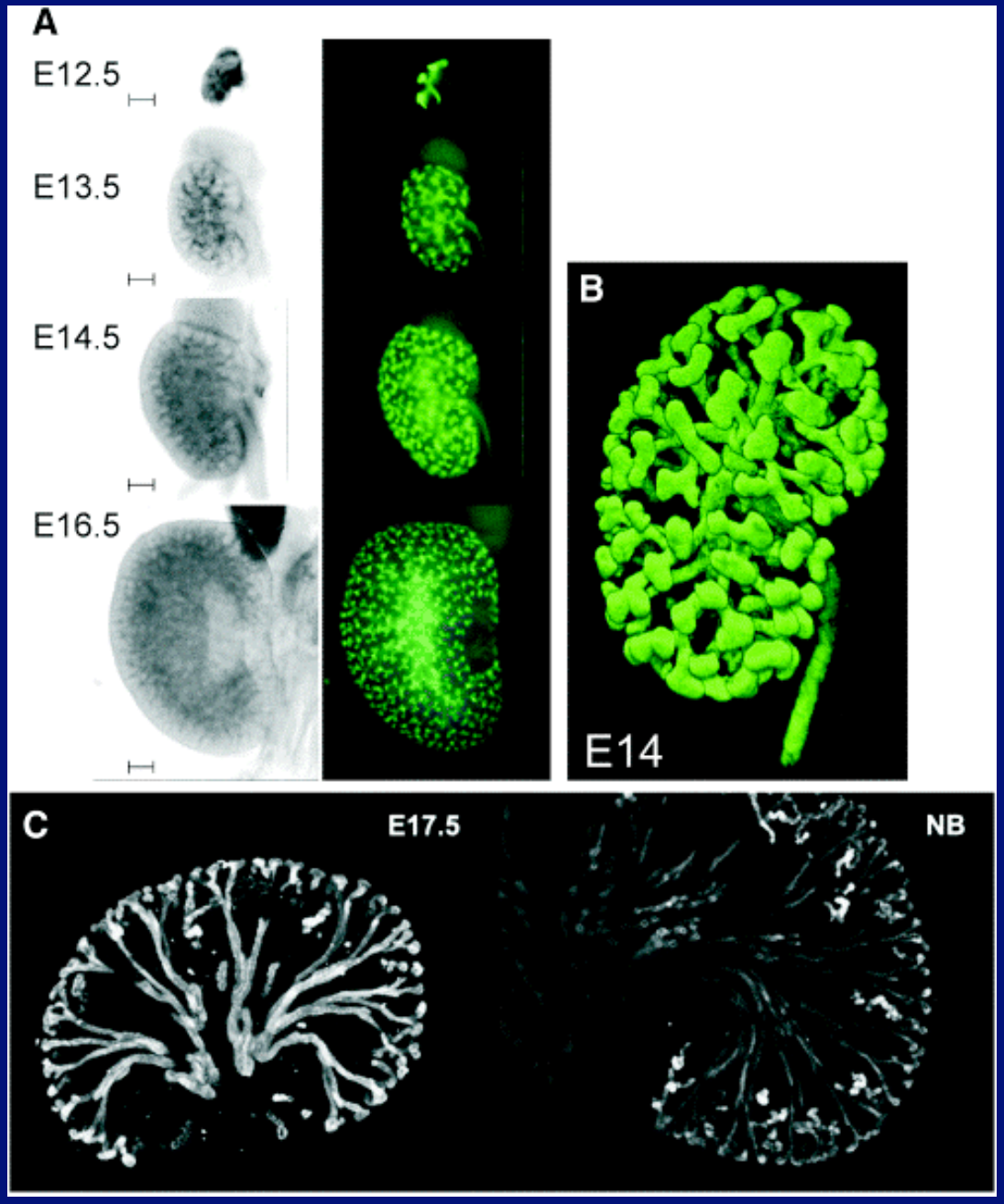
- Mesenchyme induces ureteric bud to branch.
- Bud epithelium induces condensation of mesenchyme and continued interaction leads to cavitation and formation of epithelium.
- Basement membrane between two structures is dissolved and they connect.







Vainio S and Lin Y. *Nature Reviews Genetics* 3; 533-543 (2002); doi:10.1038/nrg842
COORDINATING EARLY KIDNEY DEVELOPMENT: LESSONS FROM GENE TARGETING

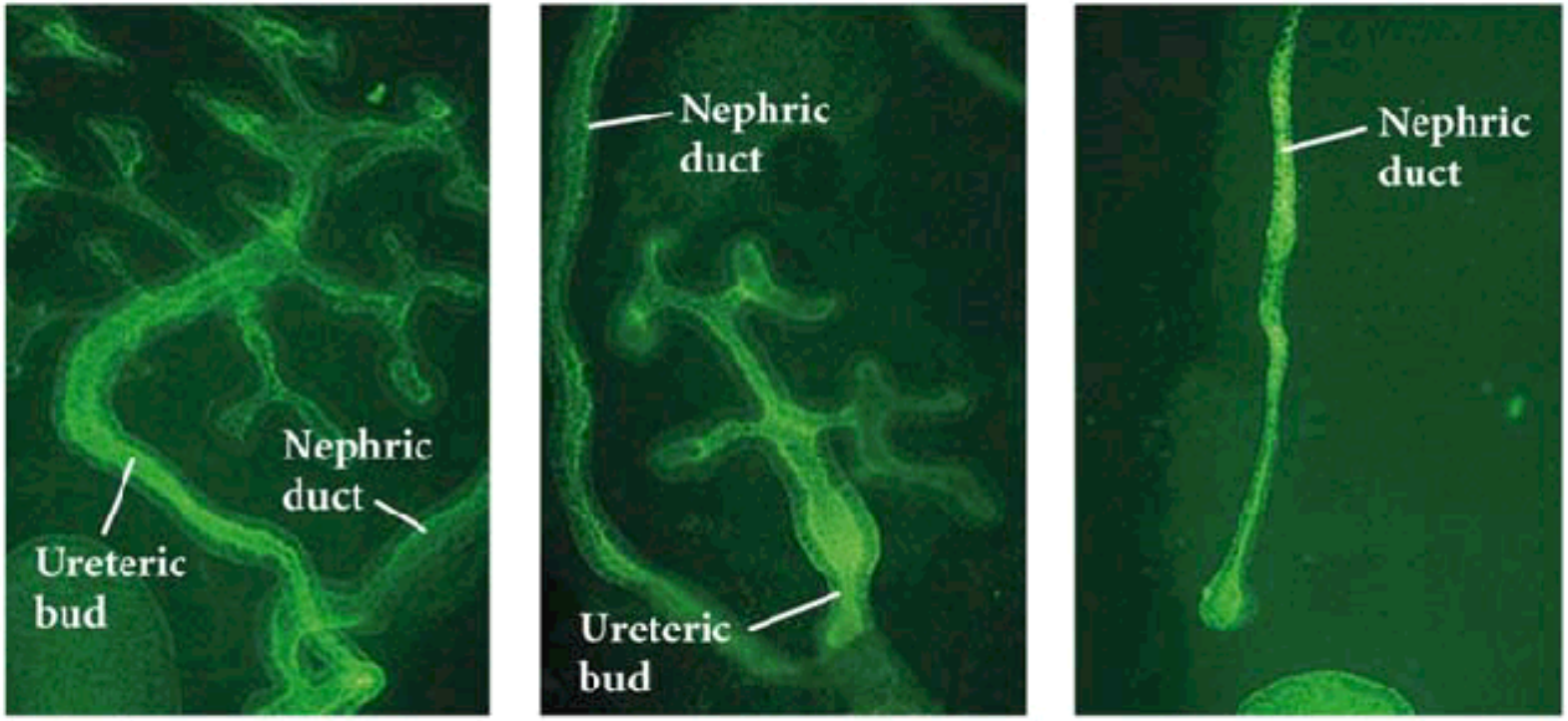


Costantini F. Differentiation 2006

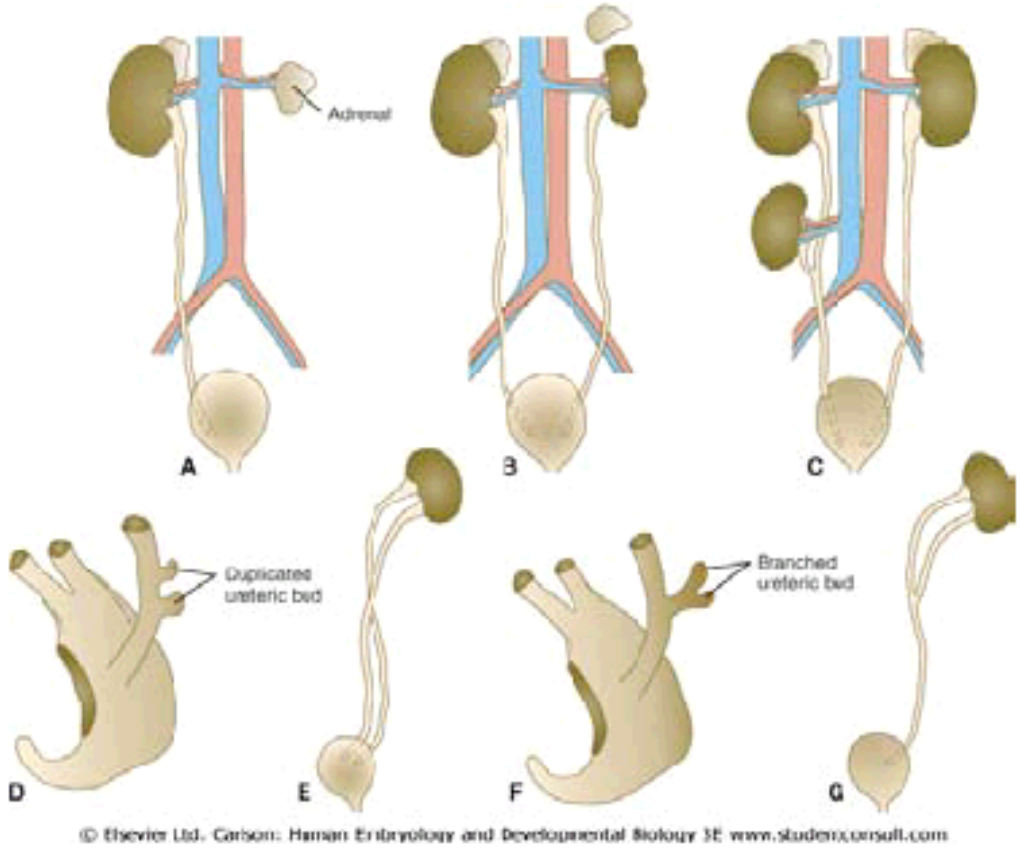
Critical role of GDNF and RET in kidney development

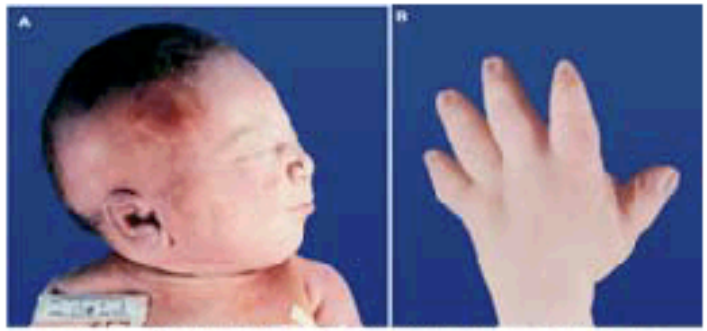
Figure 14.21(1) ***Ureteric Bud Growth Is Dependent on GDNF and Its Receptors***

- Left to right: normal, reduced GDNF (heterozygote), GDNF-knockout



Congenital Anomalies of Renal System





- Anomalies of renal system are fairly common (3-4% live births). Renal agenesis less so (0.1%) usually due to faulty interactions between metanephric mesenchyme and ureteric bud.
- Infants with bilateral renal agenesis (0.03%) die shortly after birth. Lack of urine output leads to lack of amniotic fluid (oligohydramnios) and characteristically show Potter faces (flattened nose, wide interpupillary distance, large low-set ears, receding chin) due to mechanical pressure of uterus.
- (A) unilateral renal agenesis, (B) unilateral renal hypoplasia, (C) Supernumerary kidney, (D, E) complete ureter duplication, (F,G) partial ureter duplication.

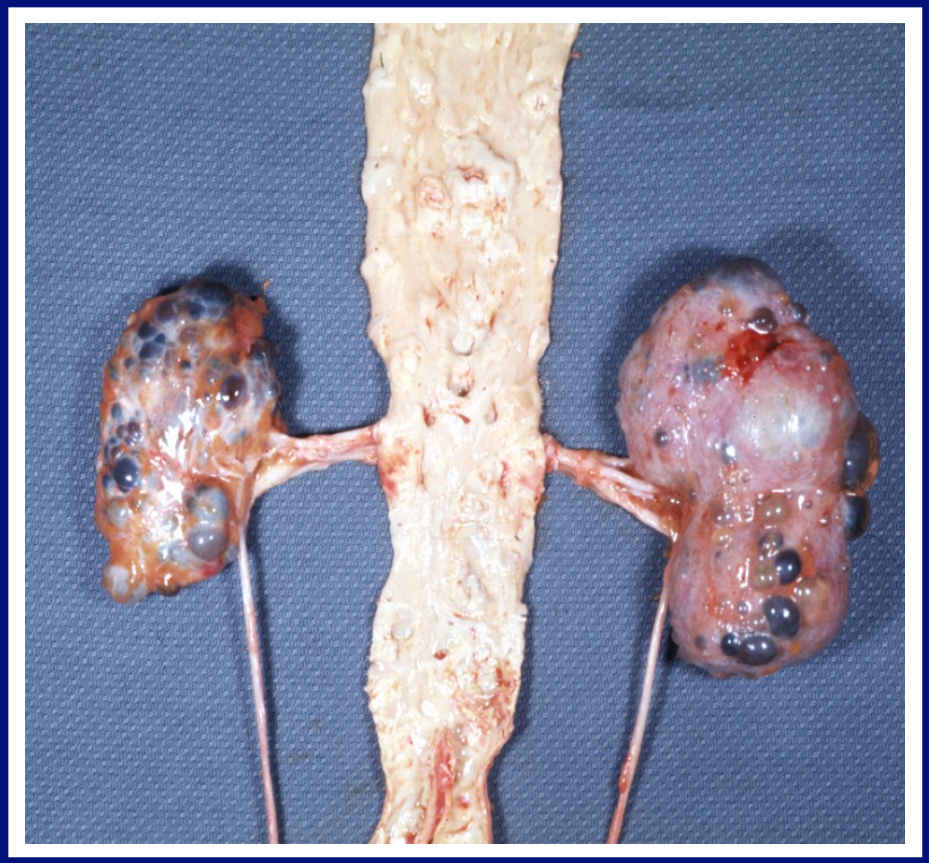
Epidemiology of Urinary tract Abnormalities

- Account for one-third of birth defects
- 40% of pediatric end-stage renal disease
- 10% of adult end-stage renal disease in some countries
- Etiology poorly understood because of variable expression and incomplete penetrance

Clinical Features

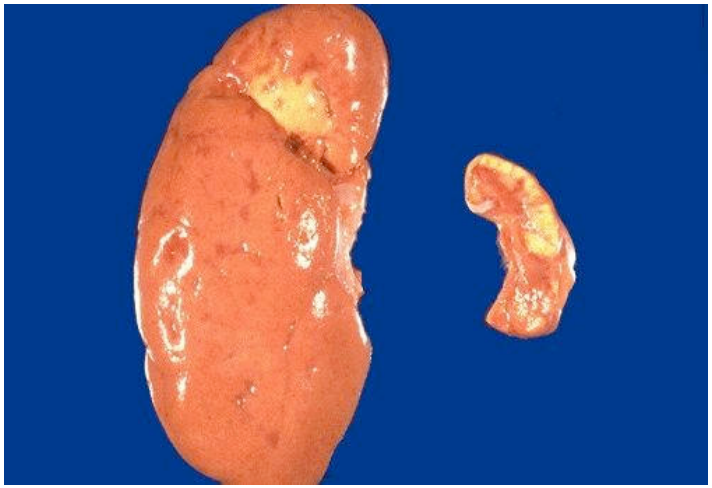
- Due to overlap between developmental pathways, phenotypes are complex, involving anatomic defects in both upper and lower urinary tract
- Often asymmetric
- Severe phenotypes result in perinatal death due to pulmonary hypoplasia
- The majority of cases are nonsyndromic

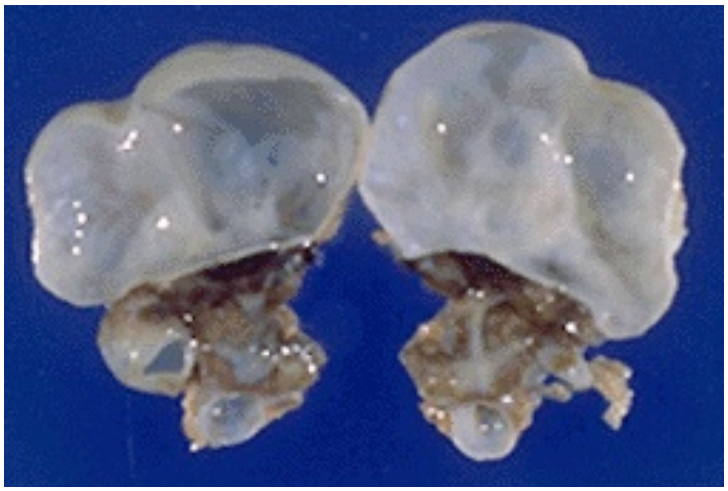
Polycystic Kidney Disease



- Major inherited disease of the kidney
- Multiple Renal cysts that invade and destroy renal parenchyma
- May be resent in-utero or develop in later in life
- Lower urinary tract defects very rare

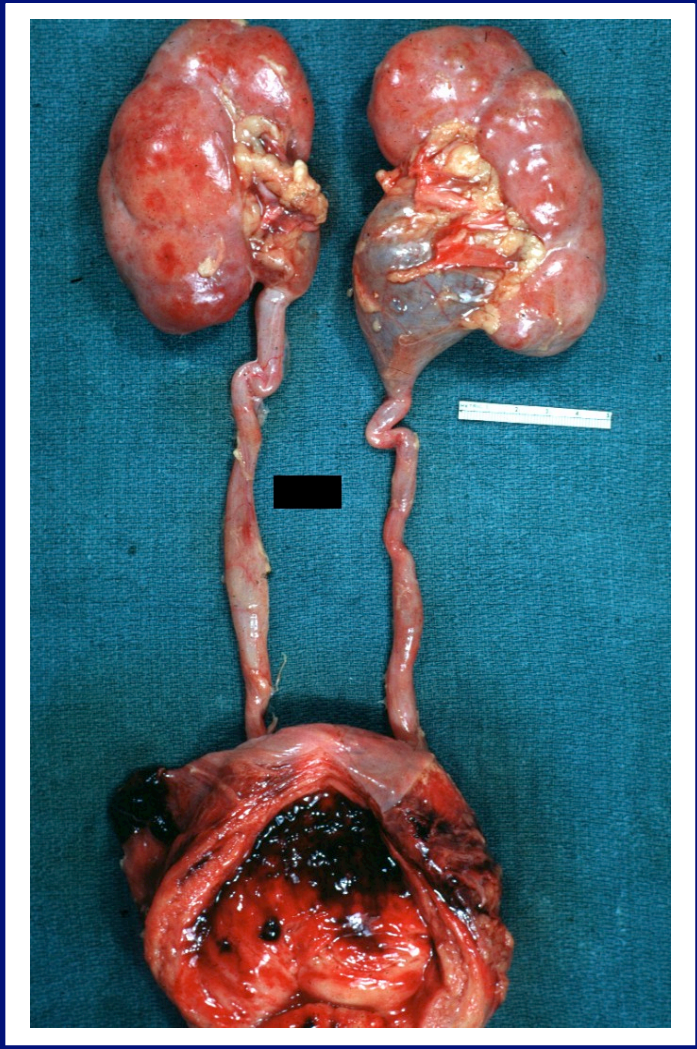
Renal Agenesis, Hypoplasia, Dysplasia





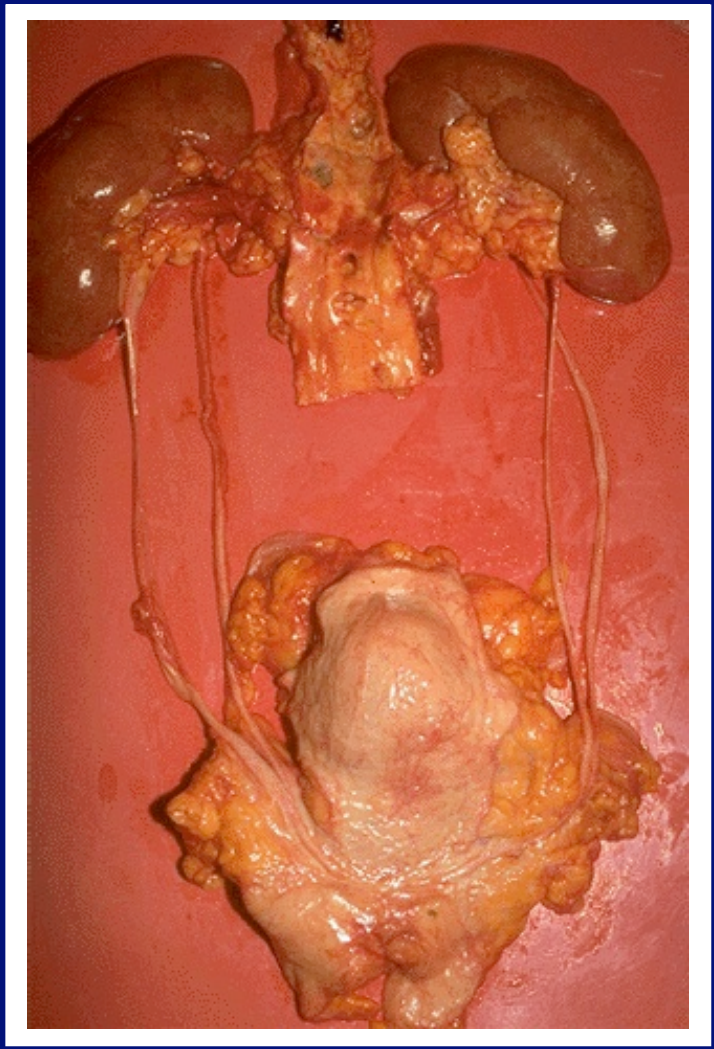
- Renal agenesis: kidney is absent
- Renal dysplasia: kidney contains undifferentiated tissues and may be small (aplasia) or distended by cysts (multicystic cystic dysplastic kidneys)
- Renal hypoplasia: kidney contains formed nephrons but significantly fewer than normal
- Associated with ureteric defects such as VUR

Ureteropelvic Junction Obstruction/ Hydronephrosis



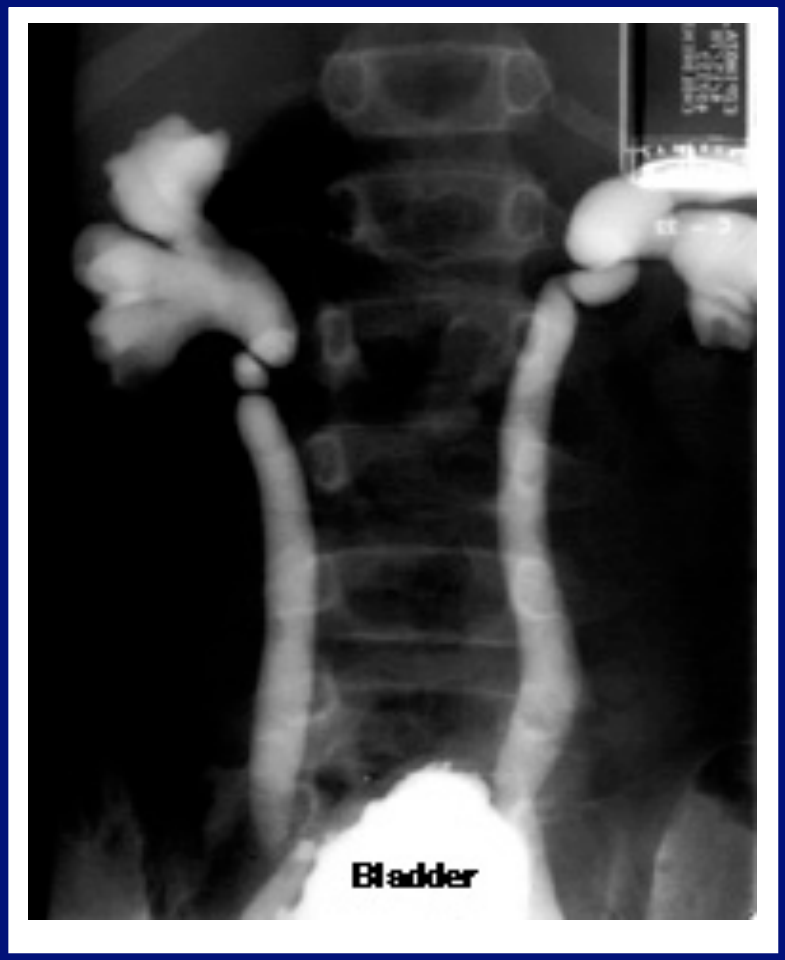
- The renal pelvis is distended and the parenchyma may be hypoplastic or dysplastic—the ureter may be refluxing or obstructed
- This can also occur as a result of mechanical obstruction (e.g. stones)

Duplicated Collecting Systems



- May full or partial, can occur in association with a duplex kidney, UPJ obstruction or vesicoureteral Reflux
- Asymptomatic kk

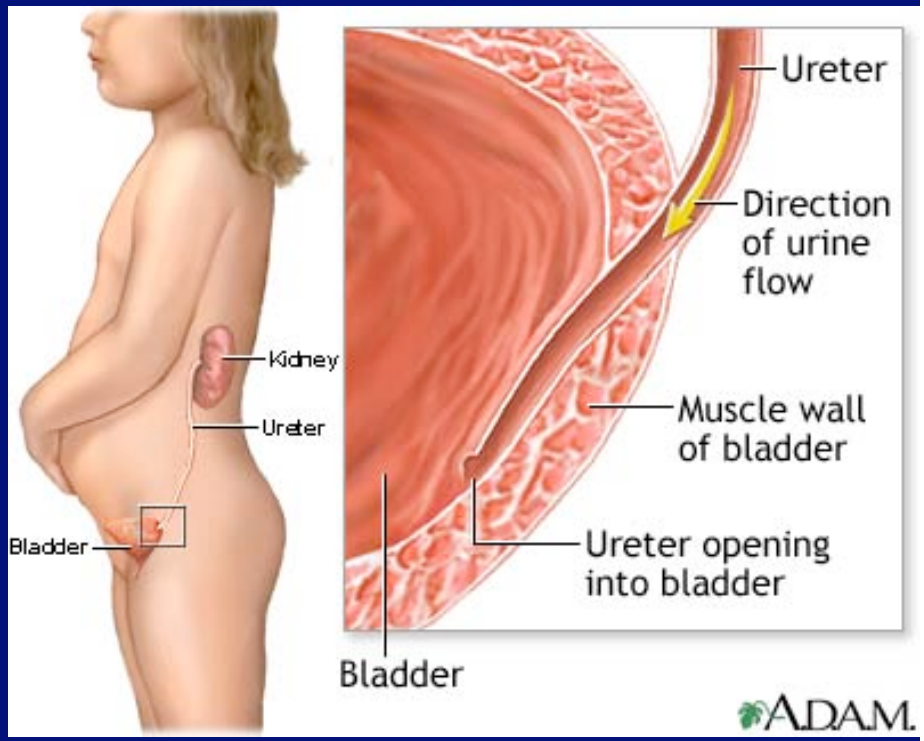
Vesicoureteral Reflux



- Backflow of urine from the bladder into the ureter, pelvis and medullary collecting ducts of the kidney
- Can occur in isolation or in conjumction with other malformations

Vesicoureteral Reflux (VUR)

- 1% of population prevalence
- Presents with UTI, enuresis
- Diagnosis by VCUG (invasive)
- Associated with shortened intravesical portion of the ureter, orifice displaced laterally, lateral displacement on the bladder base, and large ureteral orifices
- Histologically, attenuation of the trigonal and ureteral musculature.
- 25% of pediatric ESRD

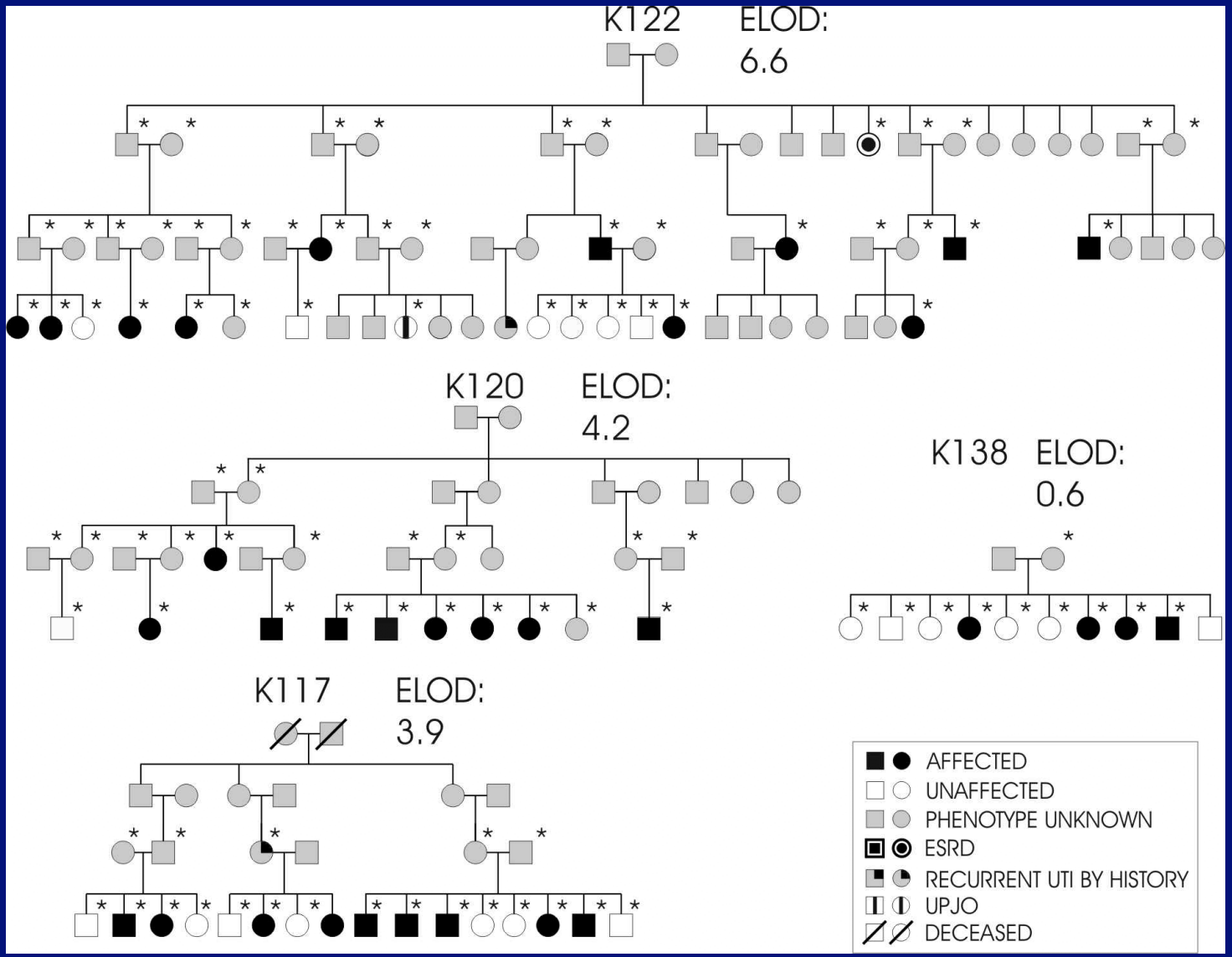


Inheritance of VUR

- Prospective screening of 354 siblings of 275 index patients with VUR revealed reflux in 119 (34%) cases
- Spontaneous resolution of VUR in patients maintained on antibiotic prophylaxis over 10 years (49-69%)
- Most urologists screen sibs, particularly age<5
- Complex inheritance

Noe J Urology, 1992, Greenfeld et al J urology J , Scott et al , Lancet 1997

Families Segregating Primary VUR



Chromosomal abnormalities

Syndromic forms

- Associated with certain chromosomal abnormalities
  - Deletion 4q, 18q
  - Duplication 3q, 10q
- Implicate defects in multiple genes in the development of the trait
- Associated with multiple organ defects

10q deletion syndrome

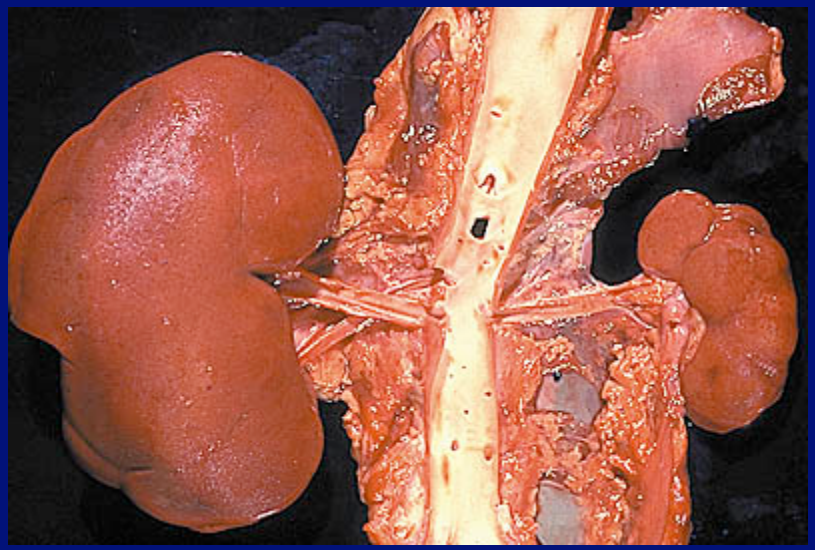
- Cardiac, urogenital, and respiratory complications, orofacial dysmorphism, and psychomotor retardation which vary with different karyotypes.
- Urogenital system: Cryptorchidism, genital hypoplasia, and streaked ovaries. Urinary anomalies include kidney aplasia or hypoplasia, hydronephrosis, hydroureter, and cystic disease.
- Systematic analysis suggest that deletion of 10q26 segment results in this phenotype

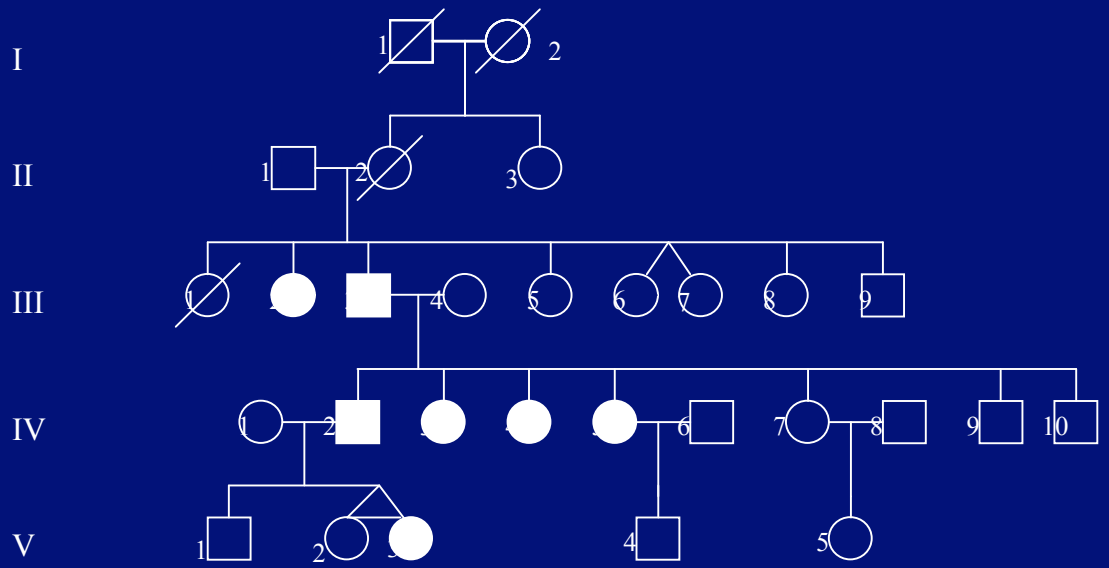
Ogata et al. Kidney Int , 2000

Single Gene Disorders in Humans

Renal Hypoplasia/Dysplasia

- Small or underdeveloped kidney
- Most common cause of pediatric kidney failure
- Most cases are nonsyndromic
- Many families with different modes of inheritance reported





III 2 : Renal agenesis (unilateral)
III 3 : Renal hypolasia
IV 2: Renal hypoplasia (unilateral)
IV 3: Renal hypoplasia (bilateral) + ESRD
IV 4: Renal hypoplasia + UPJO + VUR + ESRD
IV 5: Renal hypoplasia + UPJO + VUR + ESRD
V 2: Urinary tract infections
V 3: Renal hypoplasia

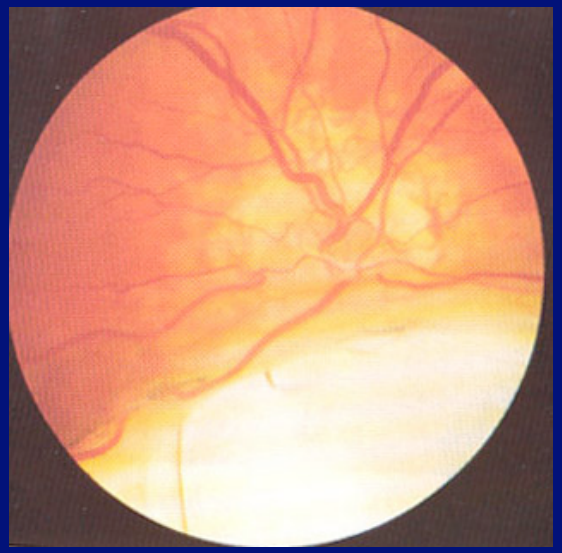
Sanna-cherchi et al. Am J Hum Gent 2007

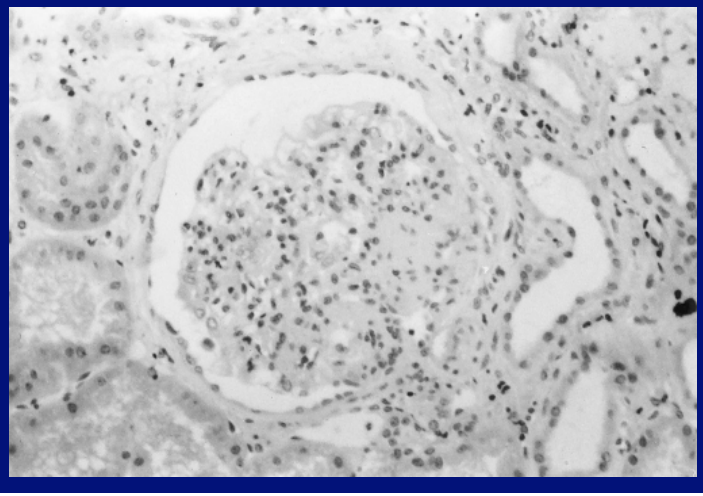
Single Gene Disorders Associated With Urinary Tract Malformations

- Renal coloboma → PAX2 mutation
- Branchiootorenal syndrome →*EYA1*, *SIX1* or *SIX5* mutations
- Renal cysts and diabetes syndrome→ TCF2 mutation
- Many Others

Renal Coloboma Syndrome

- Retinal coloboma
- Renal abnormalities that included renal agenesis, dysplasisa, VUR
- Aut. Dominant
- Caused by mutations in paired box gene 2 (PAX2)
- Can masquerade as ‘sporadic’ renal hypoplasia

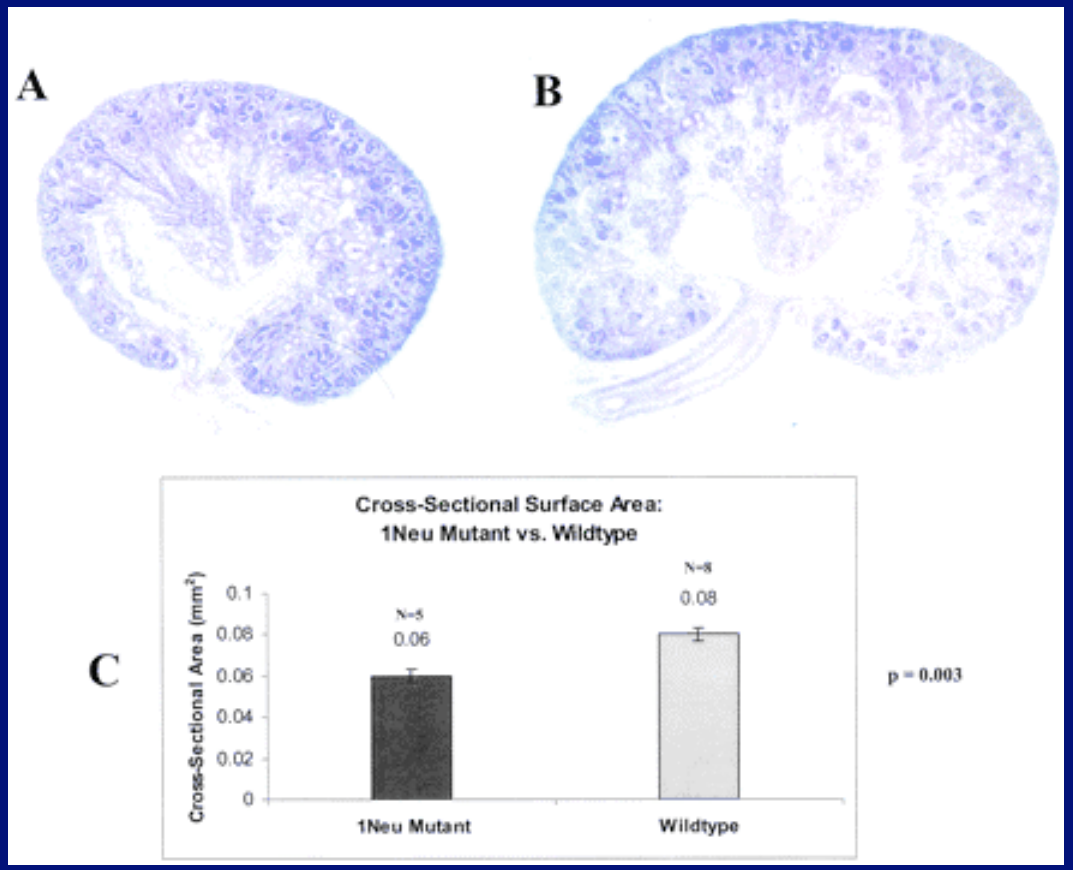


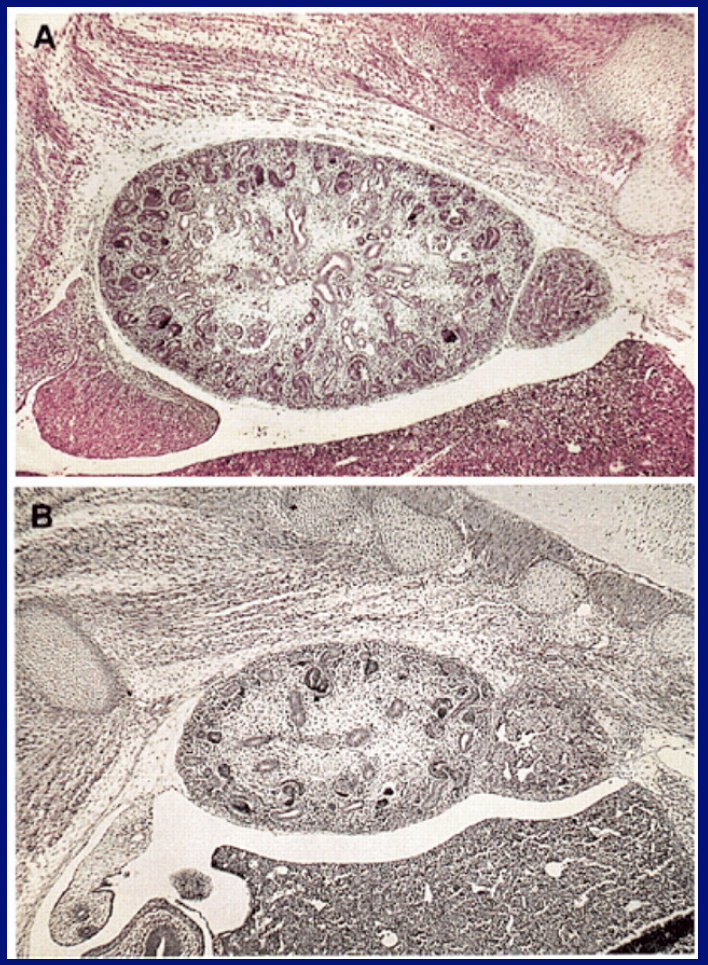


PAX2 in Renal Development

- Transcription factor
- The PAX2 gene is expressed in primitive cells of the kidney, ureter, eye, ear, and central nervous system
- During renal development, expression in nephric duct formation, then in the UB, and finally in proximal elements of the metanephric mesenchyme
- Expression absent in adult kidney

Reduced Nephrons in PAX2 Null Mice





Decrease in the rate of new nephron induction

Porteous et al, HMG, 2000, Clark et al , JASN 2004

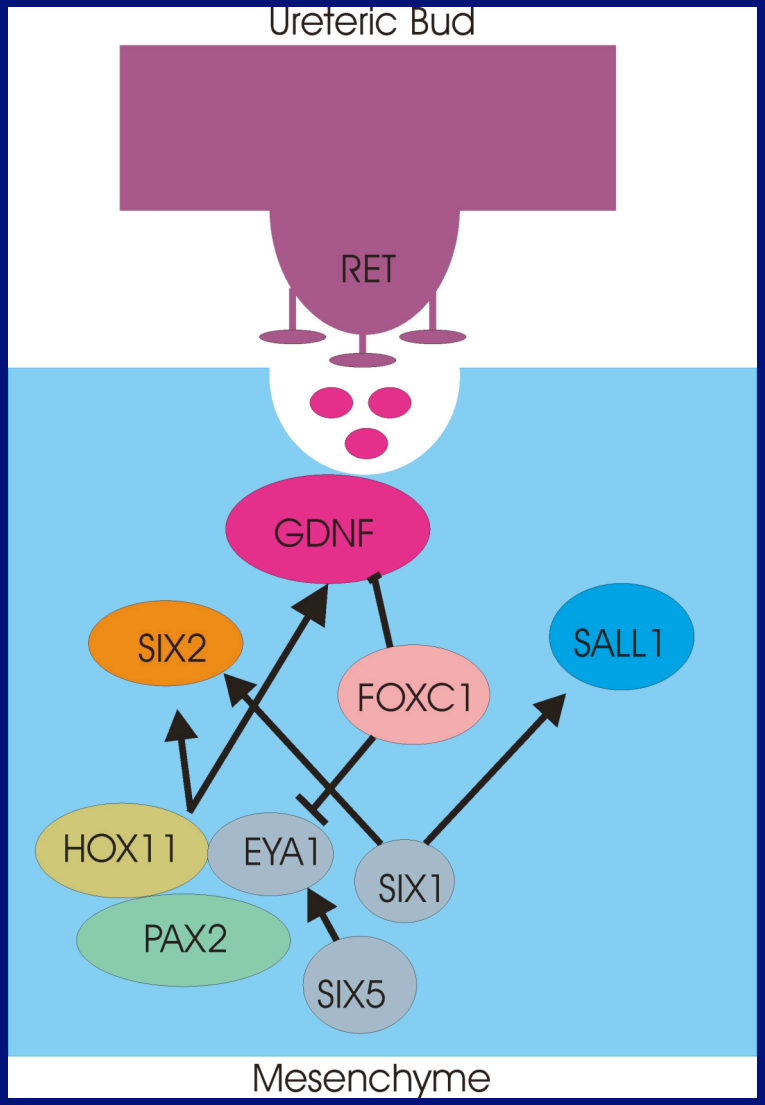
Genes Implicated in Renal Hypoplasia/dysplasia

Table 2 List of human malformation syndromes with kidney hypoplasia/dysplasia

Gene	Human syndrome	Kidney phenotype	OMIM
JAG1, NOTCH2	Alagille syndrome	MCDK, kidney dysplasia, kidney mesangiolipidosis	#118450 #610205
BBS1-BBS11	Bardet-Biedl syndrome	Renal dysplasia and calyceal malformations	#209900
EYA1, SIX1, SIX5	Branchiootorenal syndrome	Renal agenesis/dysplasia	#113650
SOX9	Campomelic dysplasia	Diverse renal malformations	#114290
CHD7	CHARGE syndrome	Diverse urinary tract malformations	#214800
Del. 22q11	Di George syndrome	Renal agenesis, dysplasia, VUR	#188400
GATA3	Hypothyroidism, sensorial deafness, renal anomalies (HDR)	Renal agenesis, dysplasia, VUR	#146255
DNA repair	Fanconi anemia	Renal agenesis	#227650
FRAS1, FREM2	Fraser syndrome	Renal agenesis, dysplasia	#219000
KALL1, FGFR1	Kallman's syndrome	Renal agenesis, dysplasia	#308700, #147950
PAX2	Renal coloboma syndrome	Renal hypoplasia, MCDK, VUR	#120330
TCF2	Renal cysts and diabetes syndrome	Renal dysplasia, cysts	#137920
GPC3	Simpson-Golabi-Behmel syndrome	Renal dysplasia, cysts	#300209
DHCR7	Smith-Lemli-Opitz syndrome	Renal dysplasia, cysts	#270400
SALL1	Townes-Brocks syndrome	Renal dysplasia, lower urinary tract malformations	#107480
LMX1B	Nail-patella syndrome	Glomerulus malformation, renal agenesis	#161200
NIPBL	Cornelia de Lange syndrome	Renal dysplasia	#122470
CREBBP	Rubinstein-Taybi syndrome	Renal agenesis	#180849
WNT4	Rokitansky syndrome	Renal agenesis	#277000
PEX-family	Zellweger syndrome	Renal dysplasia, cysts	#214100
GLI3	Pallister-Hall syndrome	Renal agenesis, dysplasia	#146510
p57(KIP2)	Beckwith-Wiedemann syndrome	Renal dysplasia	#130650
SALL4	Okihiro syndrome	Renal ectopia with or without fusion, lower urinary tract malformations	#607323
TBX3	Ulnar-Mammary syndrome	Renal agenesis	#181450

MCDK multicystic dysplastic kidney, *VUR* vesicoureteral reflux

Genes Implicated in Renal Hypodysplasia Form a Signaling Network



- Renal coloboma syndrome → PAX2 mutation
- Branchiootorenal syndrome →*EYA1*, *SIX1* or *SIX5* mutations
- Townes-Brocks syndrome → SALL1 mutations

Cystic Kidney Disease

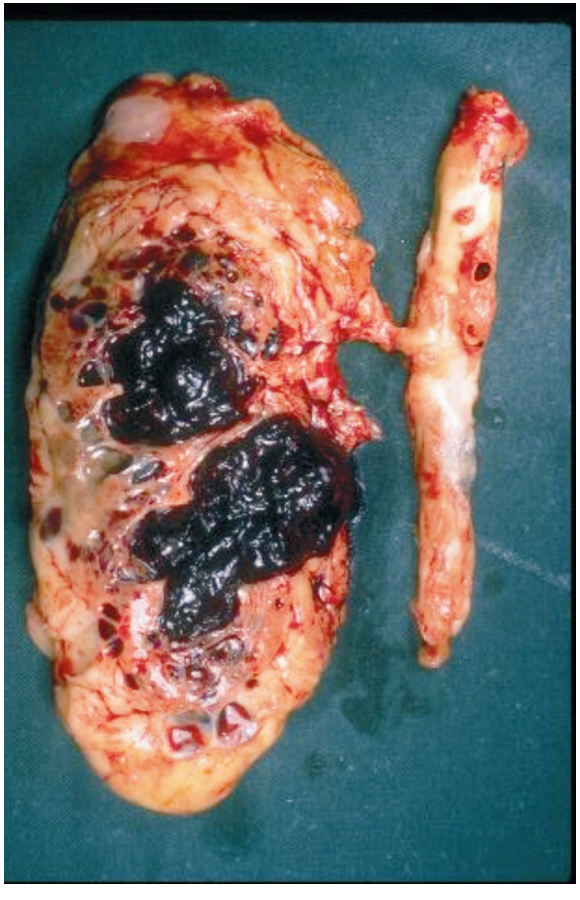
Major Subtypes

- Autosomal Dominant Polycystic Kidney Disease
- Autosomal Recessive Polycystic Kidney Disease
- Multicystic Dysplastic kidney (MCDK)
  - Diabetes and renal cysts syndrome
- Medullary Cystic/Nephronophthsis
- Bardet-Biedl syndrome
- Many Others

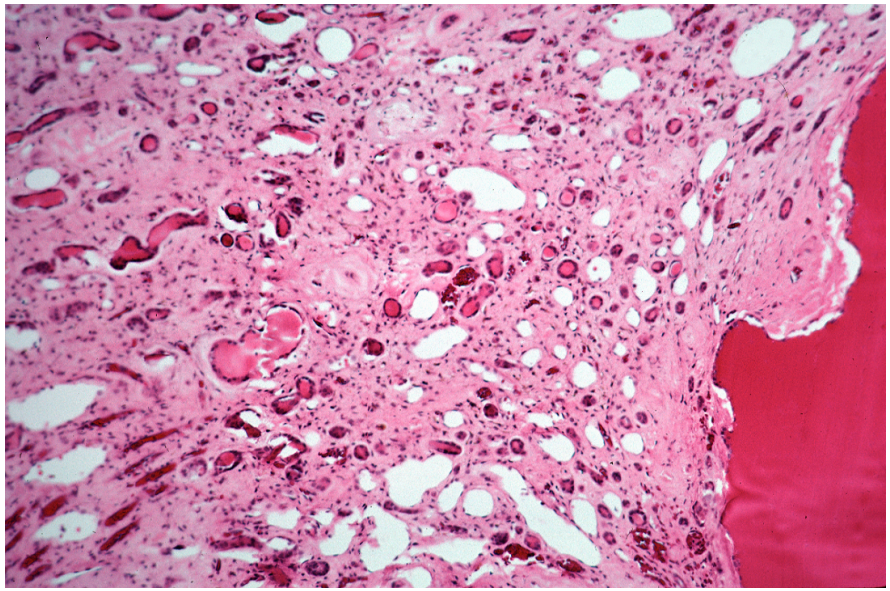
ADPKD

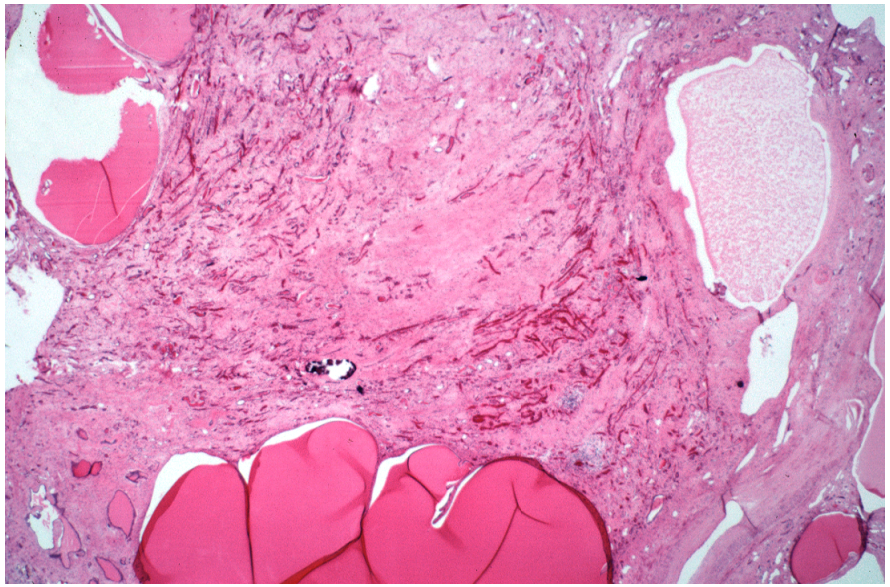
- Prevalence of 1:500 to 1:2000 in the general population
- Affects all population worldwide
- 7% of cases of end-stage renal disease in USA
- Focal and sporadic development of cysts in kidney and other organs

Pathology of ADPKD



Pathology of ADPKD

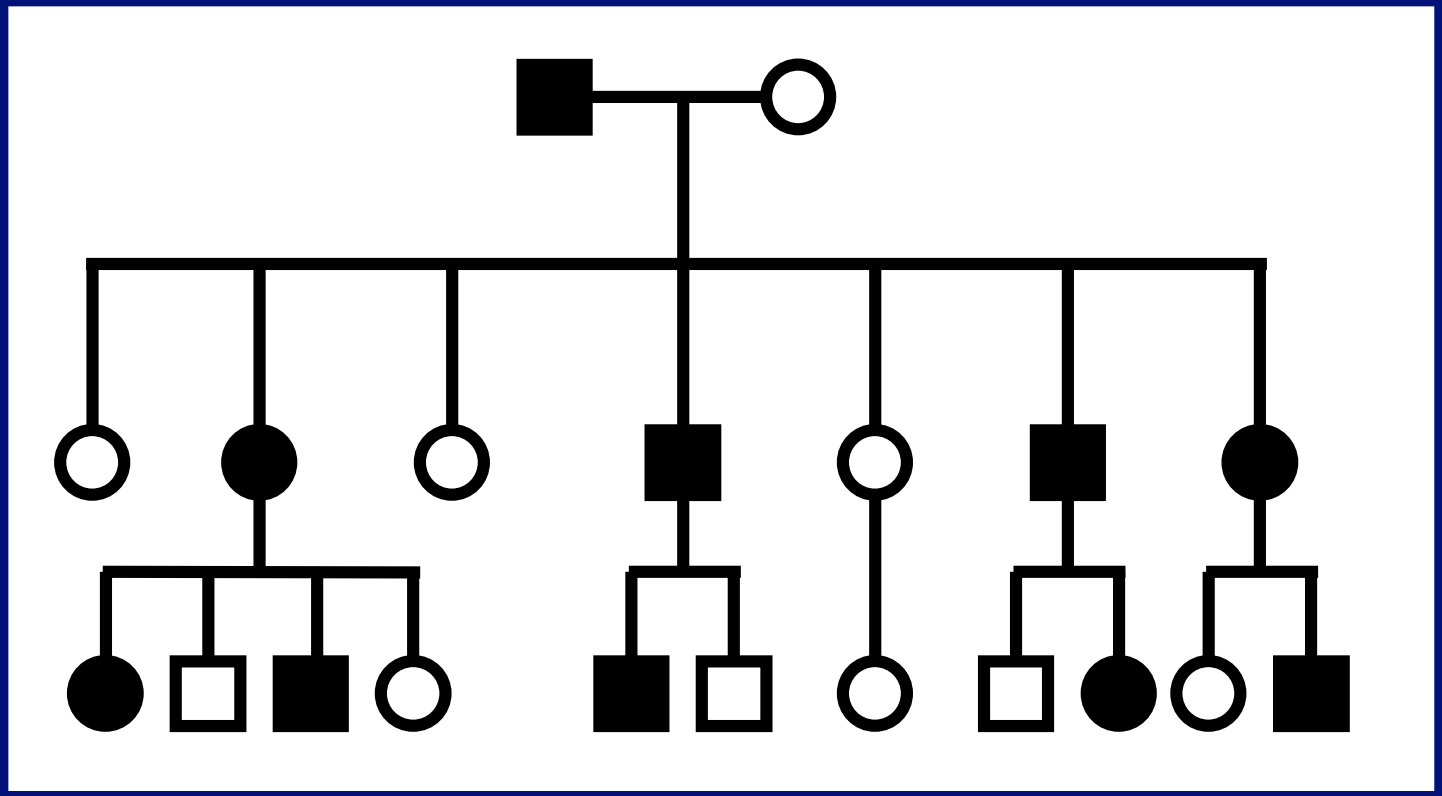




Diagnosis

- Most patients manifest very few cysts before age 30, but disease is usually overt by age 50
- 3-5 fold enlargement of kidneys
- Clinical diagnosis: Multiple bilateral cysts and positive family history
- Differential diagnosis: ARPKD, MDCK, acquired cystic disease, rare syndromic disorders

Dominant Transmission



- Each affected has an affected parent
- 50% offspring of affected individuals are affected
- Both male and female are affected in ~ equal proportion
- Vertical transmission through successive generation

Evaluation of at Risk Family Members

Table 2. Performance characteristics of ultrasound diagnostic criteria for individuals who are born with 50% risk for PKD1[a]

Age Group (yr)	Diagnostic Criterion	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
15 to 29	At least two renal cysts (unilateral or bilateral)	approximately 96	100	approximately 97	100
30 to 59	At least two cysts in each kidney	100	100	100	100
60 or older	Four or more cysts in each kidney	100	100	100	100

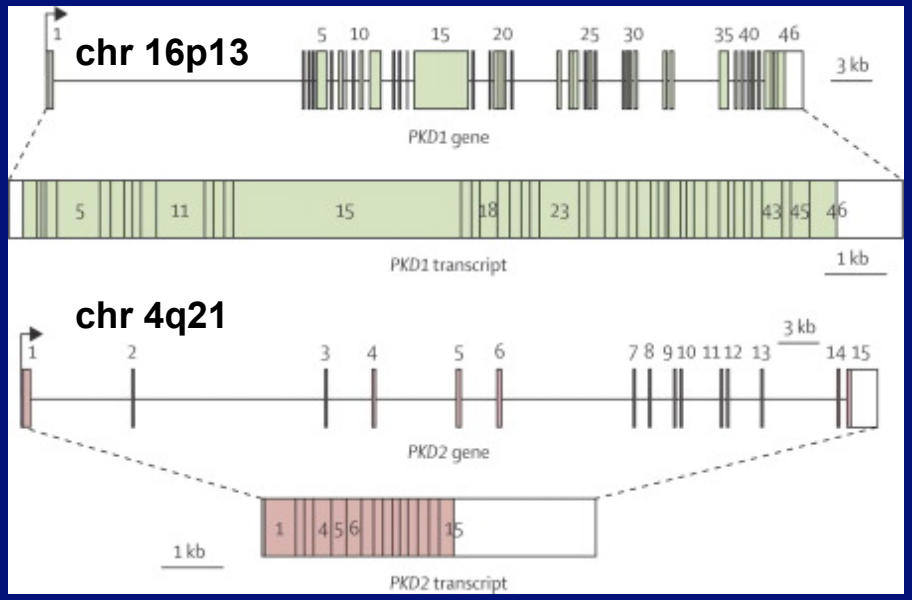
Renal Complications of ADPKD

- Early changes include concentrating defects
- Hypertension
- Pain
  - Cyst hemorrhage
  - Cyst infection
  - Stones
- Renal failure: variable progression in individuals, with about 50% reaching ESRD by age 60
  - Modified by type gene mutation, gender and hypertension

Extrarenal Complications of ADPKD

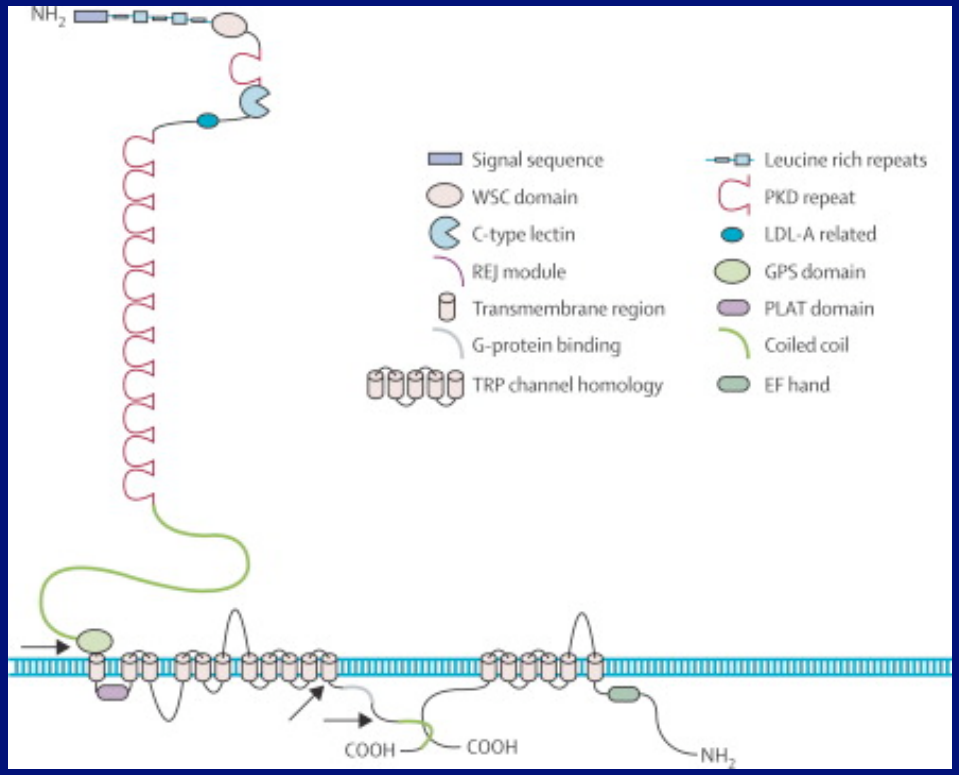
- Hepatic cysts: present in virtually all patients by age 45, but usually asymptomatic
- Cysts in other organs: pancreas, seminal vesicles, arachnoid membrane
- Intracranial Aneurysms in ~6% of cases , display familial aggregation
- Cardiac: Mitral valve prolapse, aortic insufficiency

Mutations in *PKD1* or *PKD2* cause ADPKD



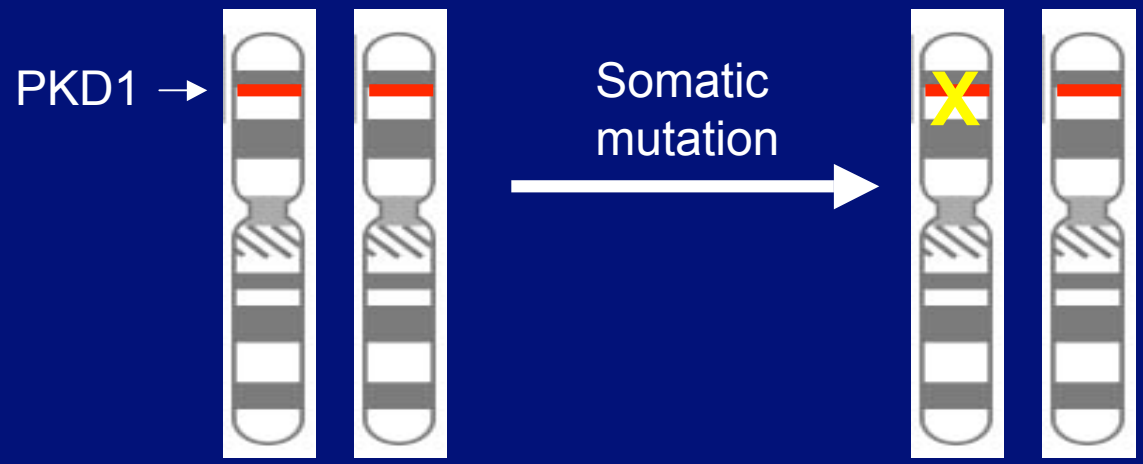
- PKD1
  - Responsible for 85% of cases
- PKD2
  - Responsible for 15% of cases
- Patients with PKD2 mutations have milder disease
- Genes are large and harbor a large number of unique variants , complicating DNA diagnostics

Function of Polycystins

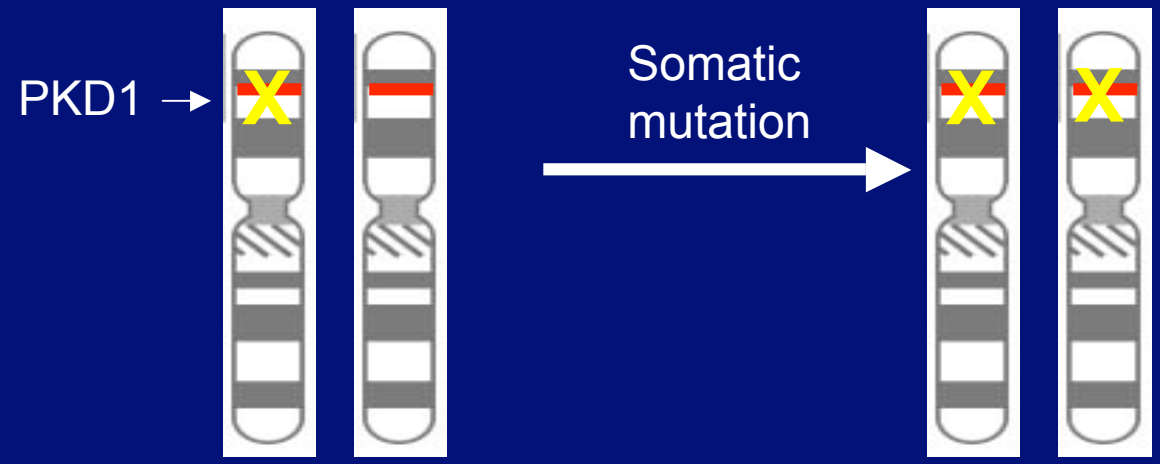


- PKD1 and PK2 interact and form a Ca channel
- Hypothesized to form receptor for a for a yet-unknown ligand

Loss of Heterozygosity



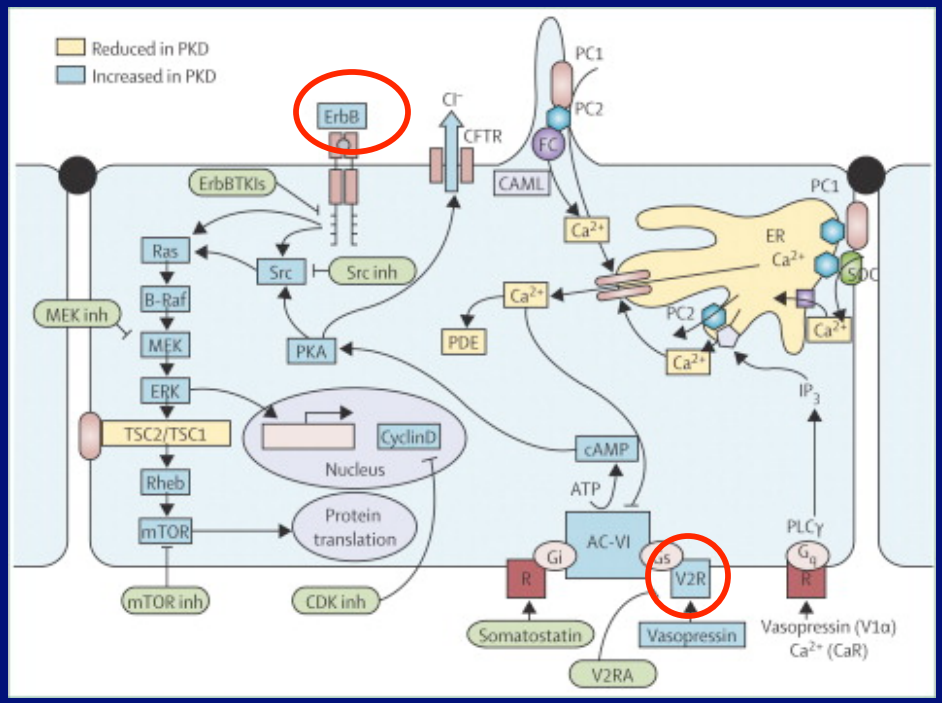
Normal phenotype



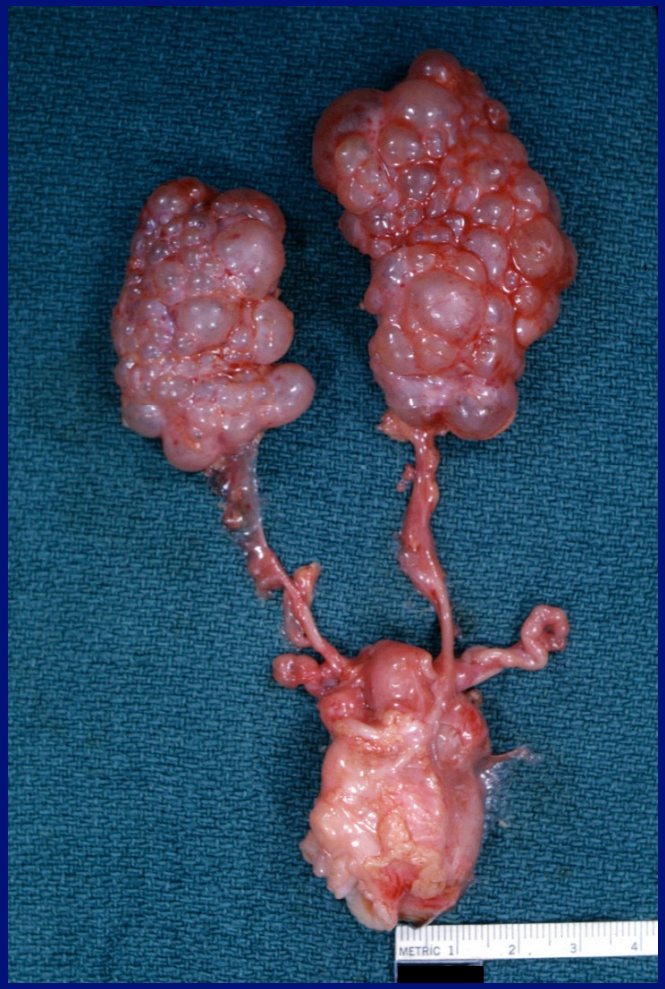
Cystic phenotype

Loss of Polycystins Produces Molecular and Phenotypic Defects in Renal Tubular Cells

- Dedifferentiation
- Increased proliferation and apoptosis
- Loss of polarity
- Excessive fluid secretion
- Multiple cellular signaling defects that can be targeted for therapy

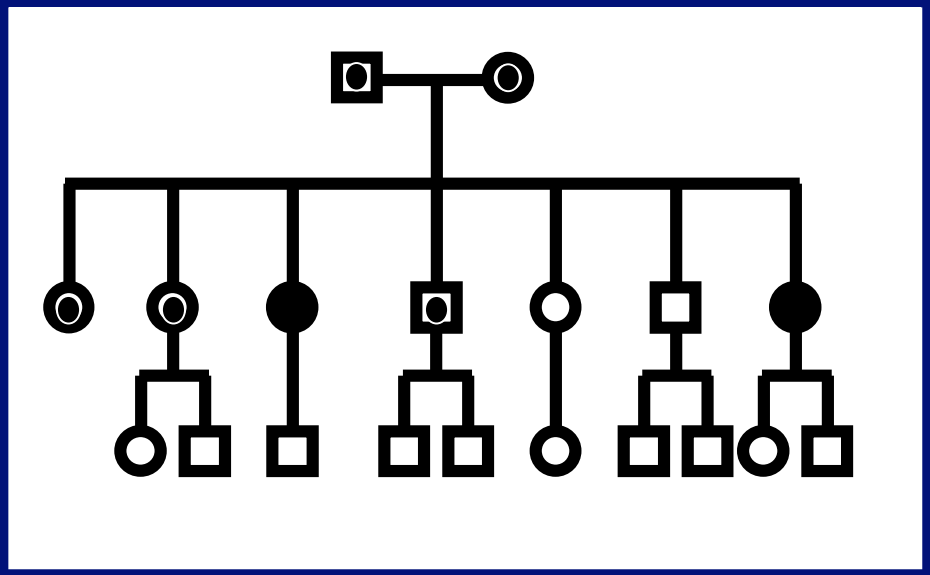


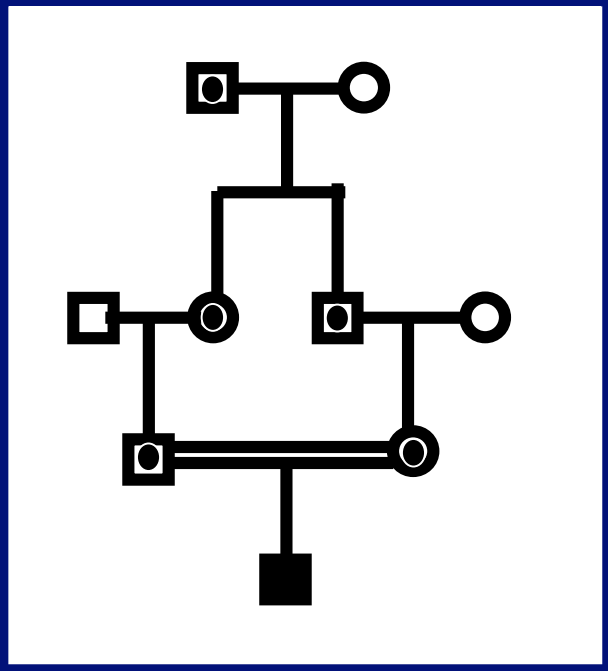
ARPKD



- One of the most common forms of pediatric renal failure
- Onset of cyst formation in-utero
- High rate of perinatal death
- Associated with severe liver cysts and liver fibrosis

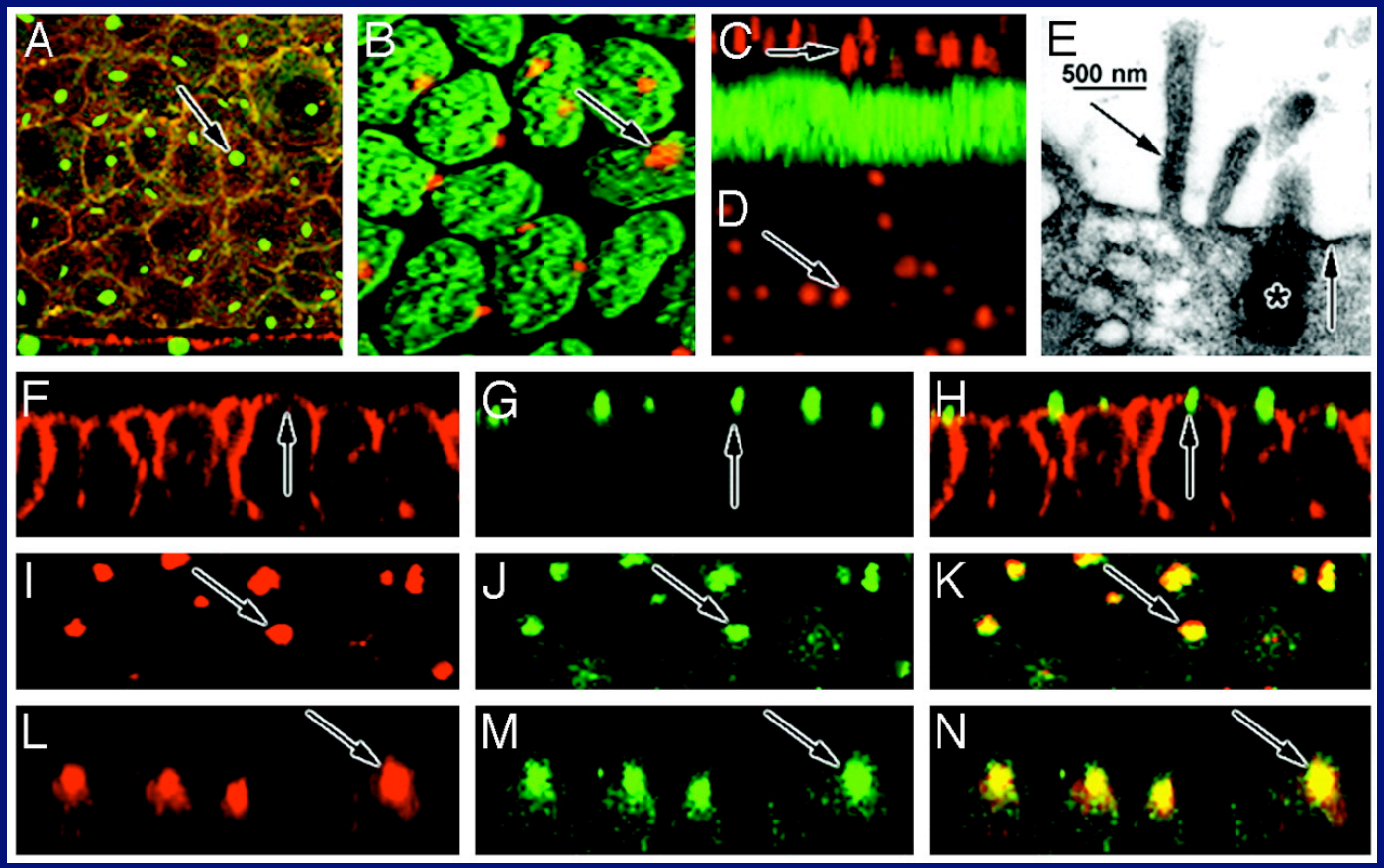
Recessive Transmission





- Parents are normal
- Only sibs are affected (a single generation)
- Usually normal male-female ratio
- 50% of children are carriers
- Increased occurrence in children
- of consanguinous unions

PKHD1 Is Associated With the Basal Bodies/primary Cilia and colocalizes with Polycystin-2

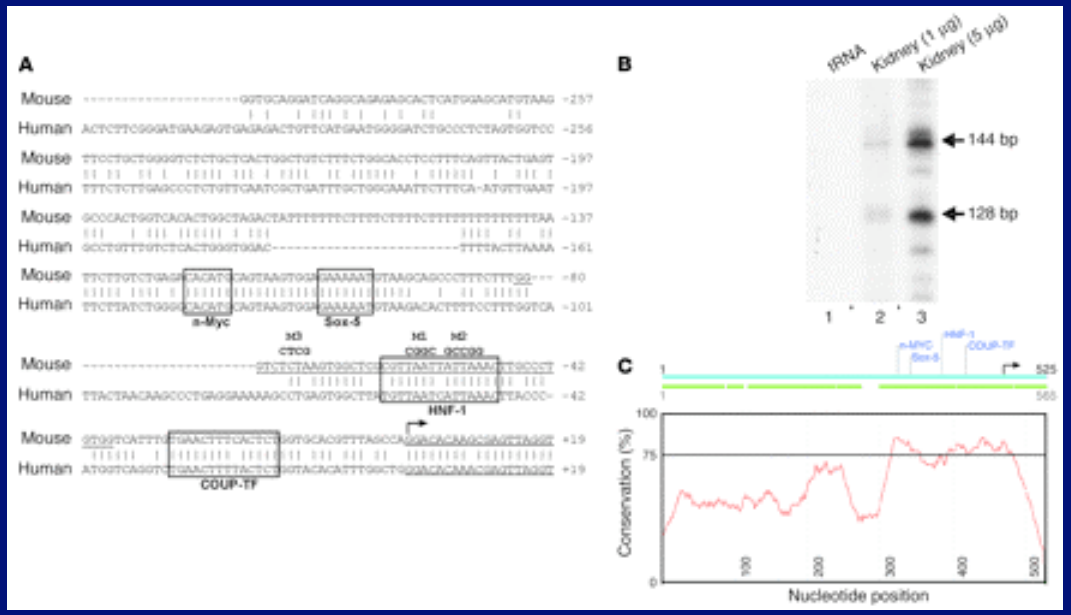


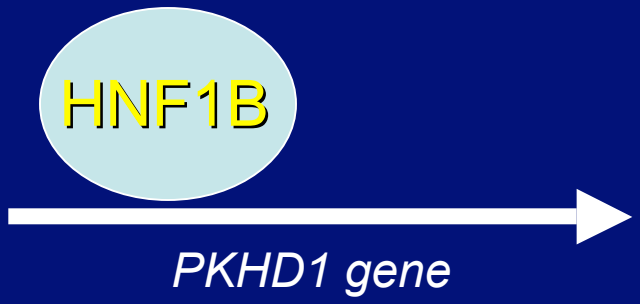
Zhang, Ming-Zhi et al. (2004) Proc. Natl. Acad. Sci. USA 101, 2311-2316

Diabetes and Renal Cysts Syndrome

- Type II diabetes in individuals <25 yrs (MODY)
- Cystic renal disease, including unilateral agenesis, horseshoe kidney, and hyperuricemic nephropathy
- Some individuals have genital malformations (e.g. vaginal aplasia, bicornuate uterus, epididymal cysts)
- Autosomal dominant transmission
- Caused by mutations in the Hepatocyte Nuclear Factor 1β (*HNF1B*)
- Can masquerade as 'sporadic' renal hypoplasia

HNF1B controls transcription of *PKHD1*

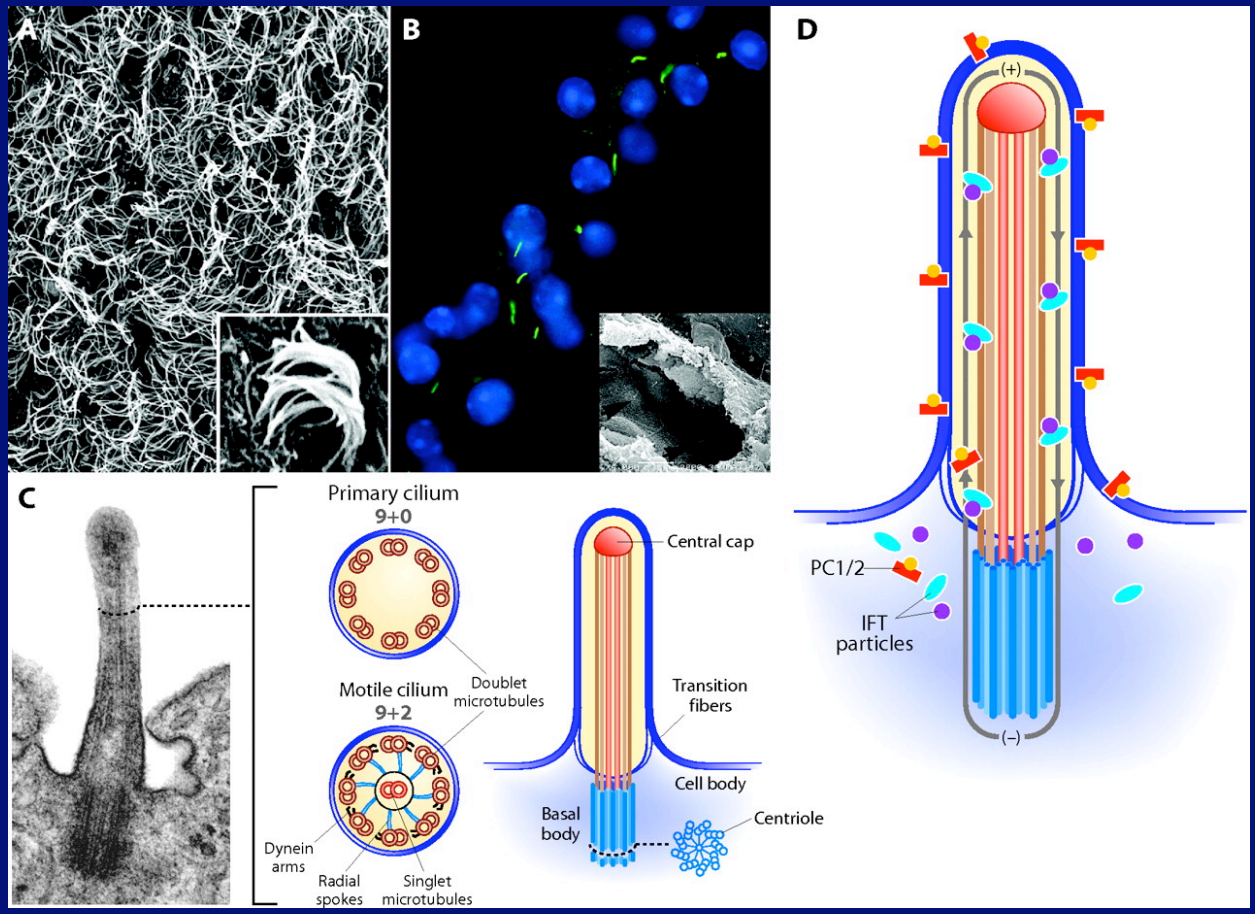




- Conserved HNF1B binding sites in PKHD1 promoter suggest that the mechanism of cyst formation in Diabetes and Renal Cysts Syndrome is due to impaired expression of *PKHD1*

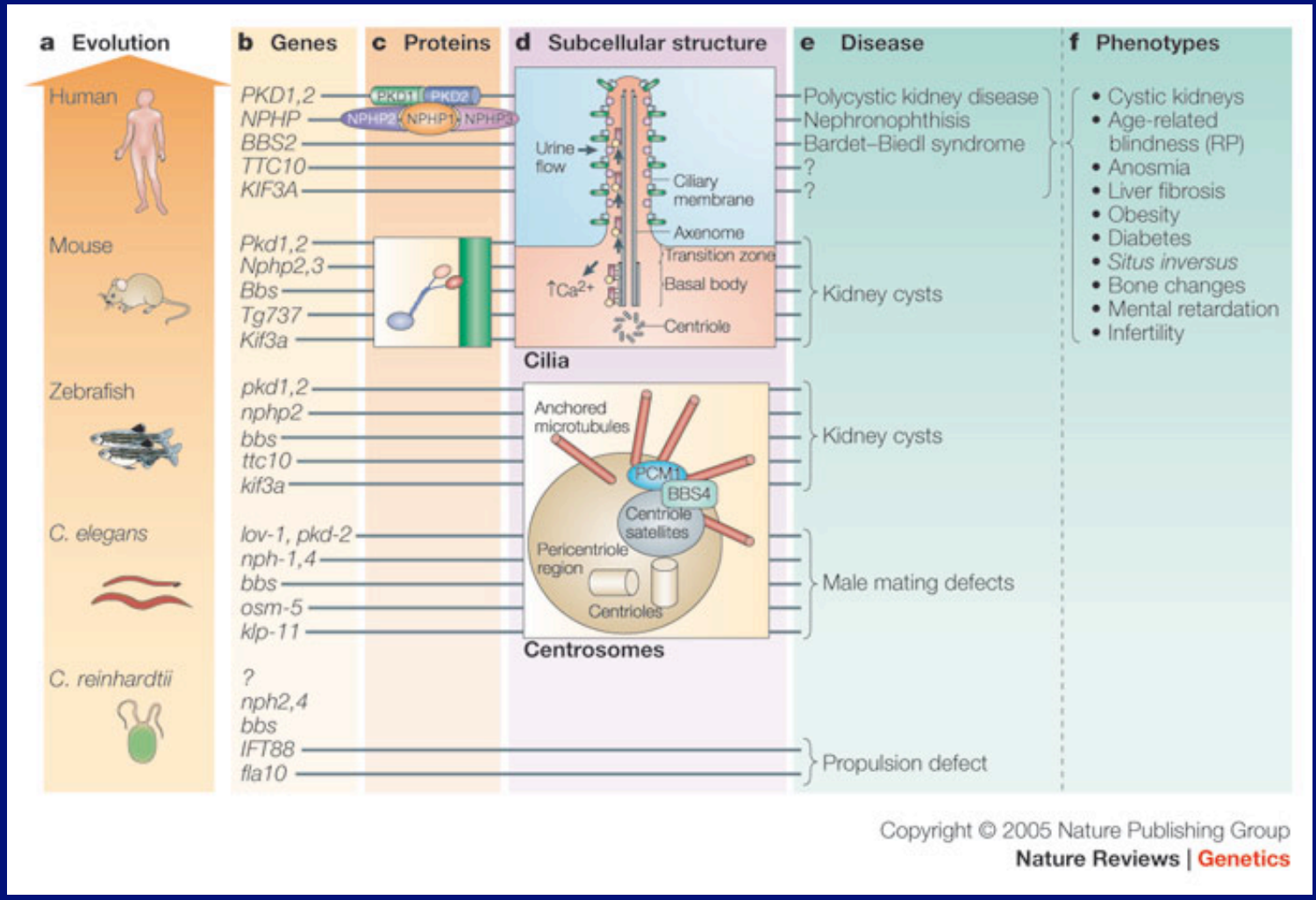
Hiesberger, T. et al. J. Clin. Invest. 2004;113:814-825

Genes Causing Cystic Diseases Localize to Primary Cilia



Yoder, B. K. J Am Soc Nephrol 2007;18:1381-1388

Genes Causing Cystic Diseases Localize to Primary Cilia



•Hildebrandt & Otto. Nature Reviews Genetics 2005 ; 6, 928

Web References

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  - Columbia Pathology: http://cpmcnet.columbia.edu/dept/curric-pathology/pathology/pathology/pathoatlas/index.html
  - Pathology Education Instructional resources (PEIR) http://peir.net/
- Human Genetics
  - **OMIM™ - Online Mendelian Inheritance in Man™**

  http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

Further Reading

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- Genetic approaches to human renal agenesis/hypoplasia and dysplasia. Pediatr Nephrol. 2007 :1675
- Torres et al. Autosomal Dominant Polycystic Kidney disease. Lancet 2007; 369:1287
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