Autosomal Dominant Tubulo-Insterstitial Kidney Disease (ADTKD)

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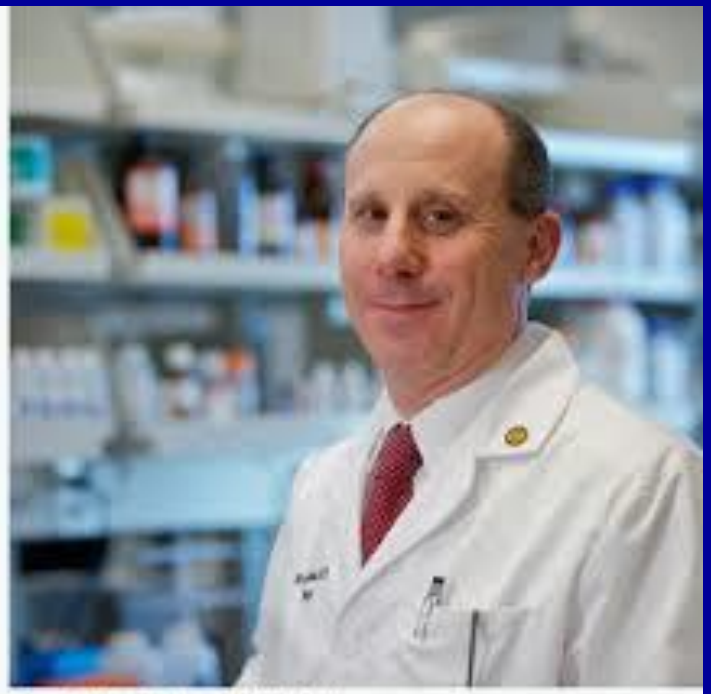
Winston-Salem, NC



Barry I. Freedman, MD, FACP

Autosomal Dominant Tubulo-Insterstitial Kidney Disease

- Medullary cystic kidney disease
- Medullary cystic kidney disease/nephronophthisis
- Familial juvenile hyperuricemic nephropathy
- Uromodulin kidney disease

Medullary Cystic Kidney Disease

- Forget about this term

- Medullary cysts are occasionally found in individuals with these conditions
  - Only seen in very advanced disease.
  - Usually not seen on ultrasound/MRI/CT
  - Sometimes seen in kidney biopsy

Tubulo-Interstitial Kidney Disease

- Not a glomerular disease
- No proteinuria
- No hematuria
- Renal ultrasound: unremarkable or small kidneys if late in the disease
- Kidney biopsy
  - Secondary glomerular changes
  - Tubular atrophy
  - No tubulointerstitial inflammaiton

Inherited Tubulo-Interstitial Kidney Disease

Autosomal Recessive

Nephronophthisis

Childhood with
ESRD < 20
CKD
Ciliopathies
Salt wasting,
anemia

Autosomal Dominant

UMOD

MCKD2
Gout (women, teens)
CKD in 3rd to 7th decade

RENIN

Anemia, hyperkalemia,
mild hypotension in
childhood

CKD in 3rd to 7th decade

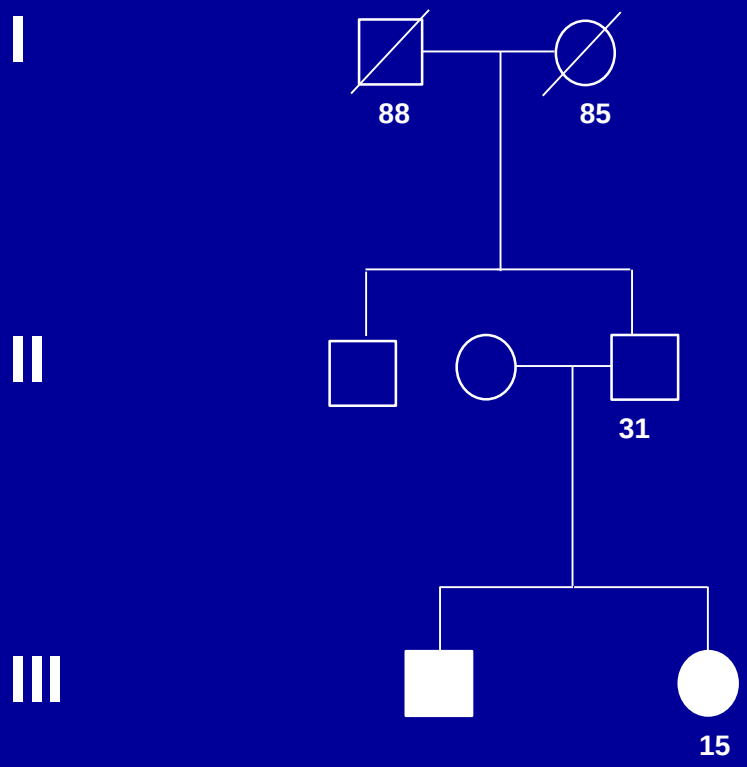
MUC1

MCKD1
CKD in 3rd to 9th decade
No other symptoms

Other

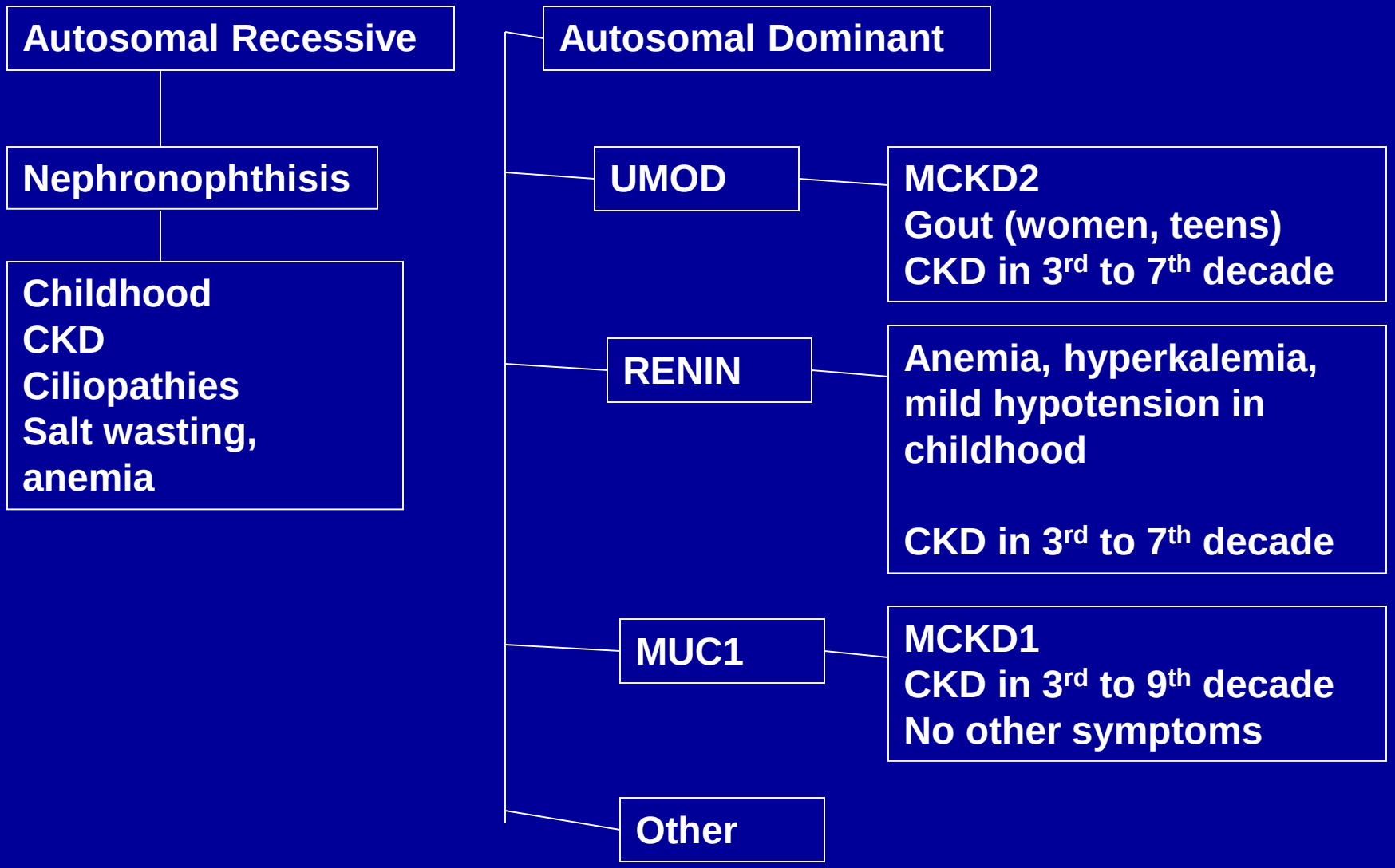
- A 15 year old presents with anemia and decreased vision
- Serum creatinine 400 mmol/l
- Urine: dipstick negative for blood, trace protein.
- Renal ultrasound small kidneys
- Neither parent with kidney disease
- A brother with kidney disease

Family 11 Pedigree



Note characteristics of autosomal dominant inheritance

Inherited Interstitial Kidney Disease



Inherited Interstitial Kidney Disease

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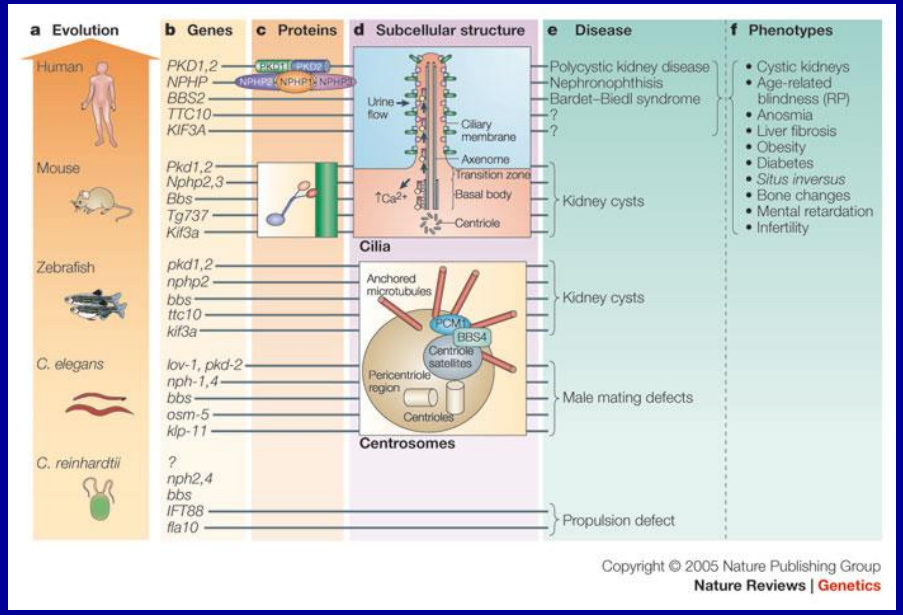
Other

Nephronophthisis

- Caused by mutations in genes expressed in the renal tubular cilia
- Slowly progressive kidney disease
- Associated with: blindness, situs inversus

Corinne Antignac, MD

Friedhelm Hlidebrandt, MD




Greetings from
NORTH CAROLINA
STATE FLOWER - DOGWOOD
STATE BIRD - CARDINAL
BOONE
BLUE RIDGE PARKWAY
BLOWING ROCK
GRANDFATHER MOUNTAIN
MT. MITCHELL
GREAT SMOKY MOUNTAIN NATIONAL PARK
ASHEVILLE
HICKORY
CHIMNEY ROCK
CHEROKEE
MURPHY
LAKE NORMAN
LAKE LURE
GASTONIA
STATESVILLE
CHARLOTTE
CAROWINDS
ROCKINGHAM
WINSTON
GREENSBORO
BURLINGTON
HIGH POINT
CHAPEL HILL
DURHAM
ASHEBORO NC ZOO
PINEHURST
RALEIGH
ROCKY MOUNT
GREENVILLE
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GOLDSBORO
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FORT BRAGG
JACKSONVILLE
CAMP LEJEUNE
NEW BERN
WILMINGTON
CALABASH
ORTON PLANTATION
CAROLINA BEACH
FORT FISHER
ELIZABETH CITY
WRIGHT BROTHERS' NATIONAL MONUMENT
KITTY HAWK
NAGS HEAD
MANTEO
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CAPE HATTERAS
CHERRY POINT
MOREHEAD CITY
FORT MACON
BEAUFORT
ELIZABETH II
MOUNT MITCHELL
HIGHEST PEAK EAST OF THE MISSISSIPPI RIVER
VENUS FLY TRAP
USS NORTH


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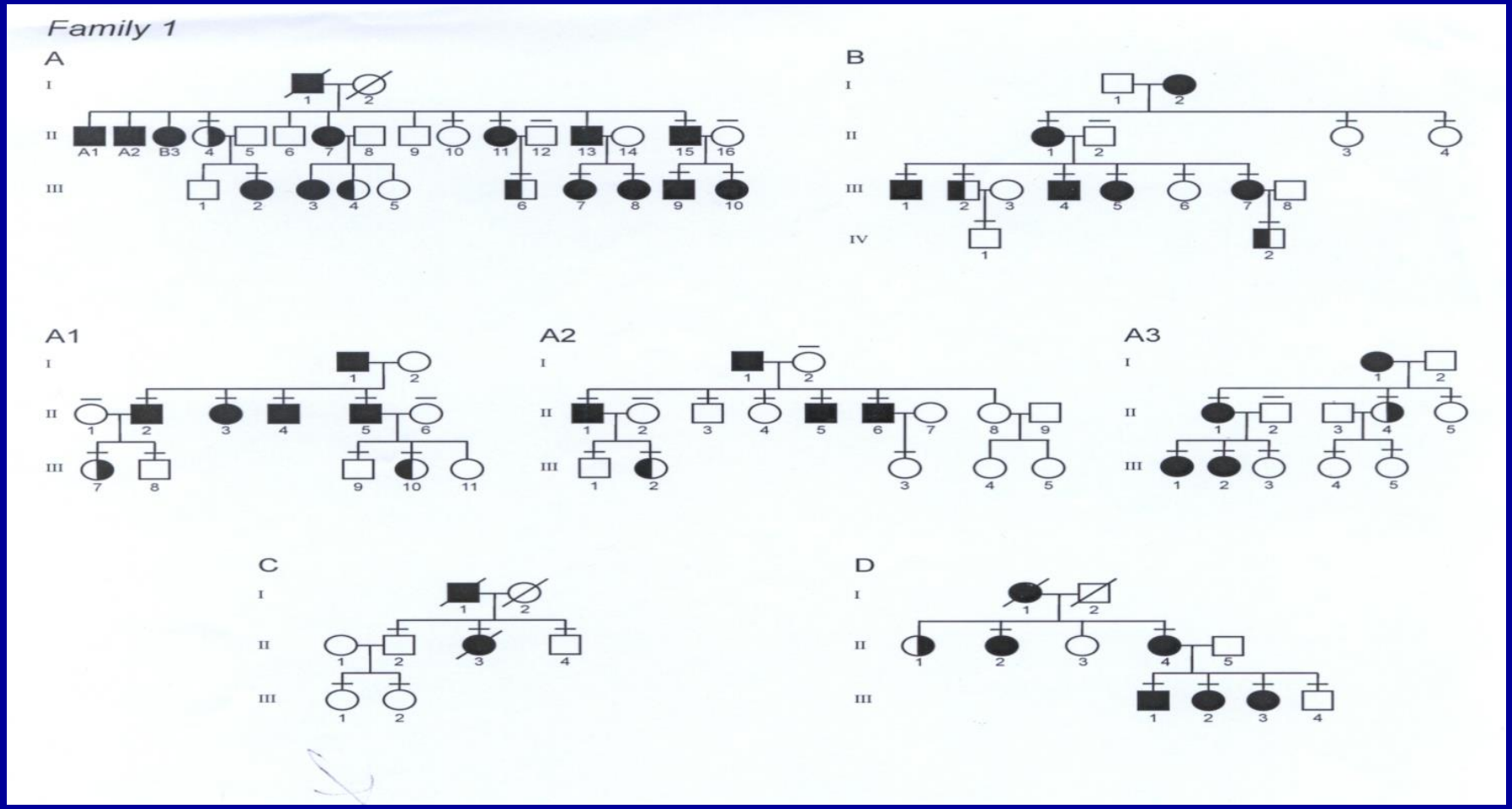
HIGHEST PEAK EAST OF THE MISSISSIPPI RIVER
VENUS FLY TRAP
USS NORTH

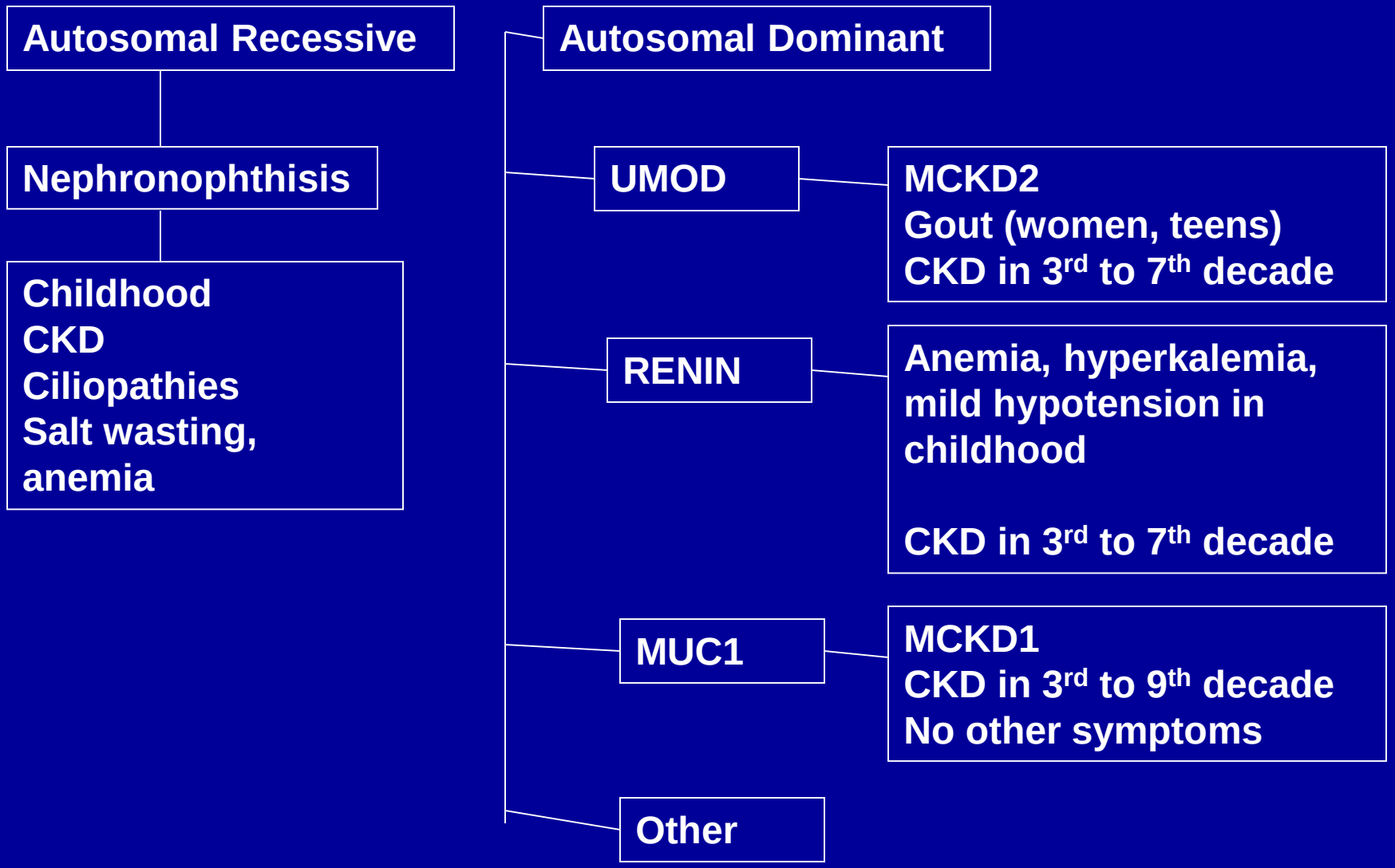
First Case 4/18/96

- 41 year old white male
  - Serum Creatinine 300 mmol/l
- Urinalysis:
  - Dipstick negative for blood
  - Dipstick negative for protein
- Renal ultrasound unremarkable

Family Tree



Inherited Interstitial Kidney Disease



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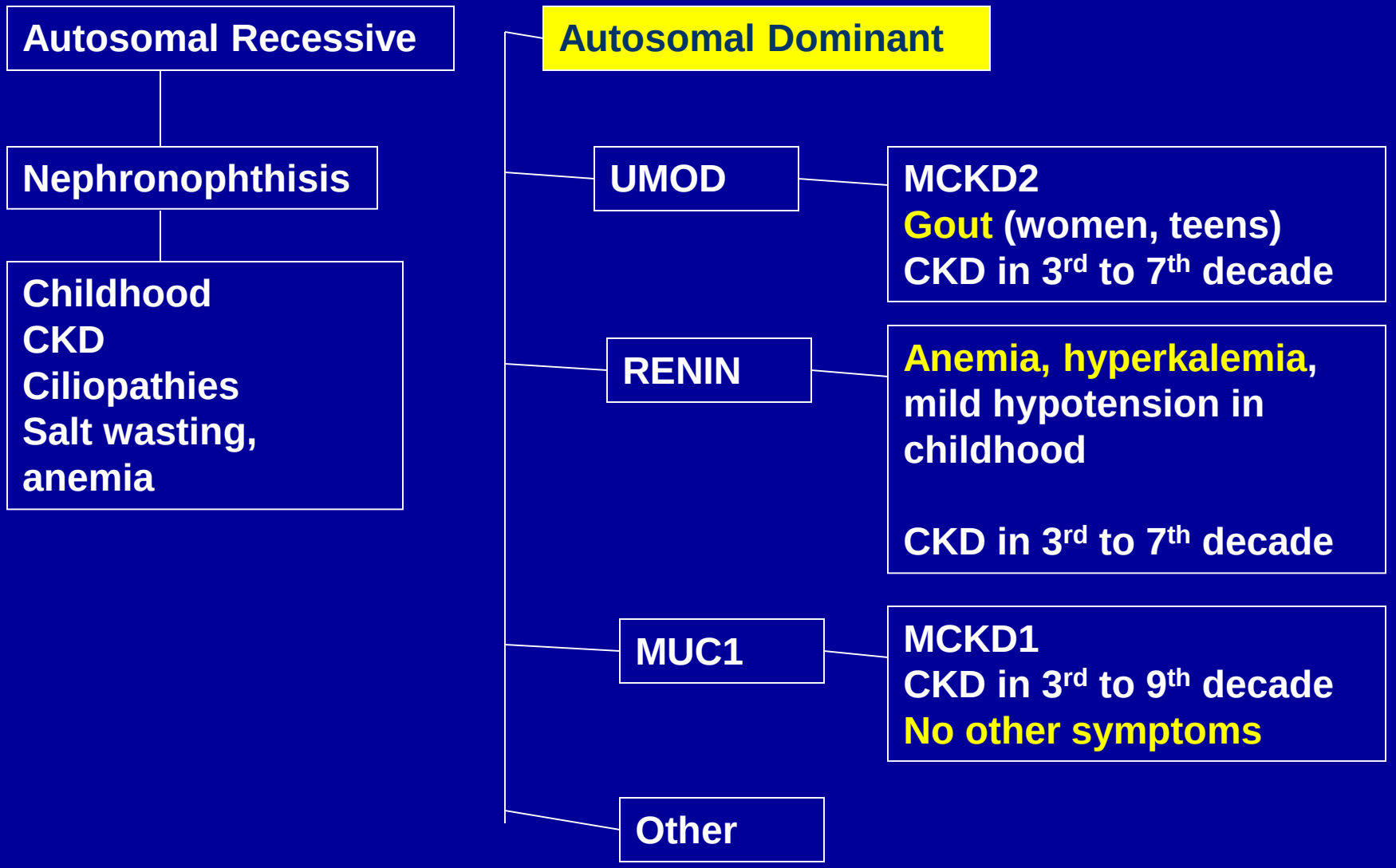
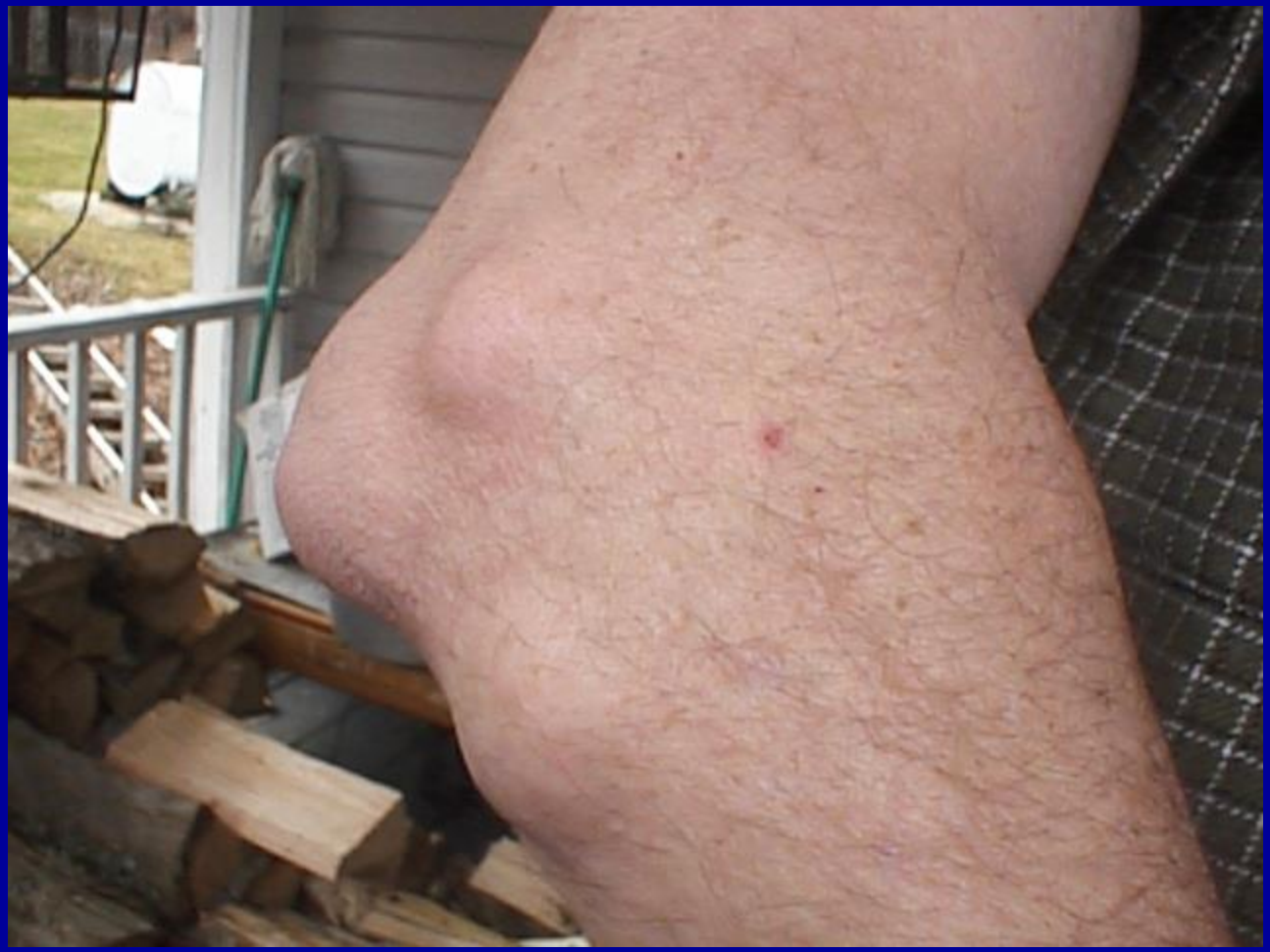


First Case 4/18/96

- 41 year old white male
  - Gout in late teens
  - Noncompliant with allopurinol
  - Development of tophi
  - Many, but not all, family members had suffered from gout
    - Women in their 30's and 40's
    - Young men in their teens
  - Gout occurred prior to onset of kidney dysfunction.



- Parents watched closely for the presence of gout, which determined the fate of their child.

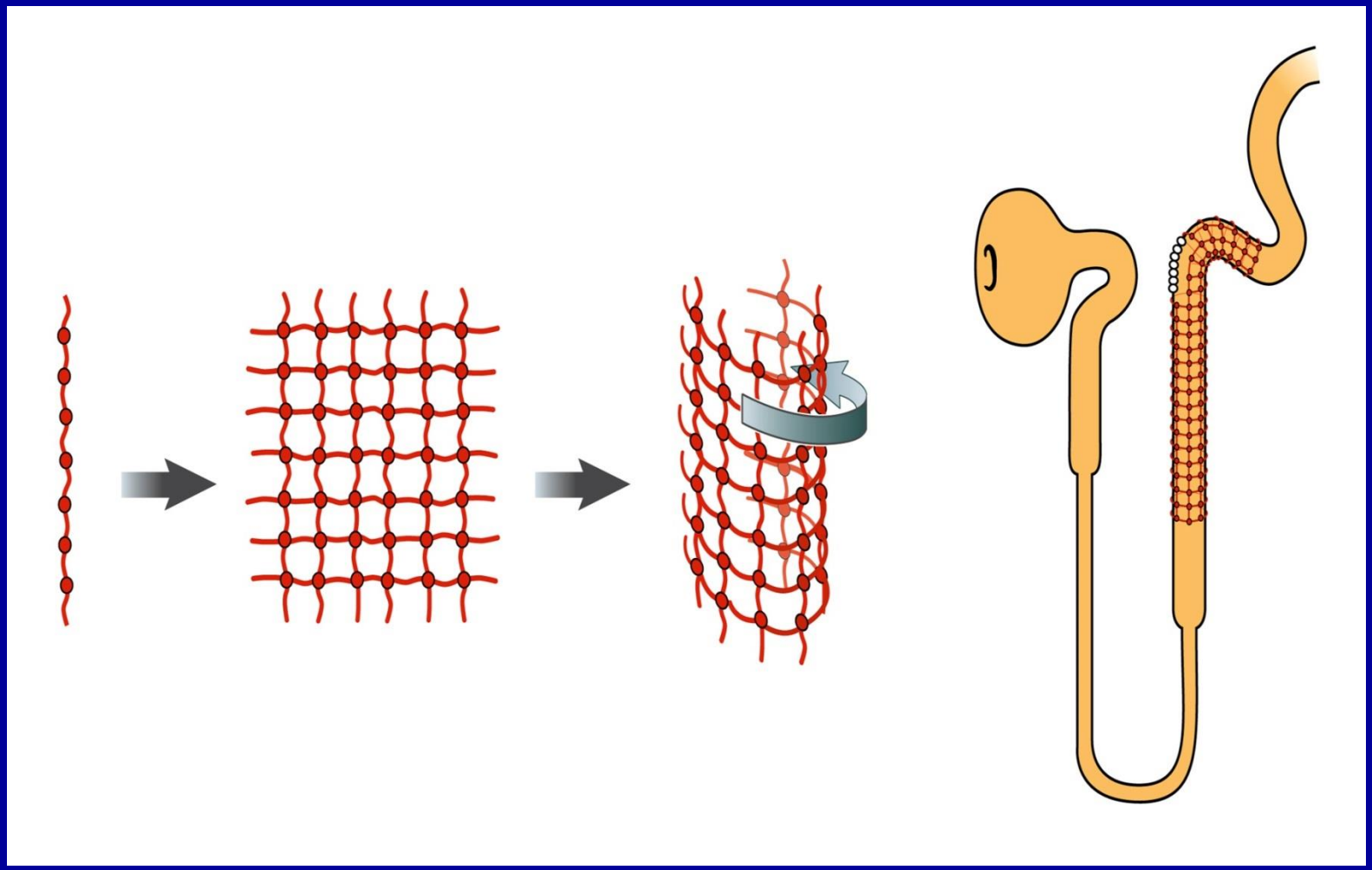
- Working with Thomas Hart, DDS, over the next six years we collected numerous samples and were able to identify mutations in the *UMOD* gene encoding uromodulin as the cause of this condition.

What is Uromodulin?

- “Tamm Horsfall Glycoprotein”
- The most common urinary protein
- Synthesized only in the thick ascending limb of Henle’s loop

Uromodulin

- The most cysteine residues of any known human protein
- Extensive cross-linking in the endoplasmic reticulum



Possible Uromodulin Functions

- Prevents urinary tract infection
- Prevents kidney stone formation
- Prevents inflammation in the kidney
- New data suggests that these are not the current functions of uromodulin in humans.

Uromodulin

- Regulates movement of bumetanide – sensitive Na K 2 Cl (NKCC2) transporter

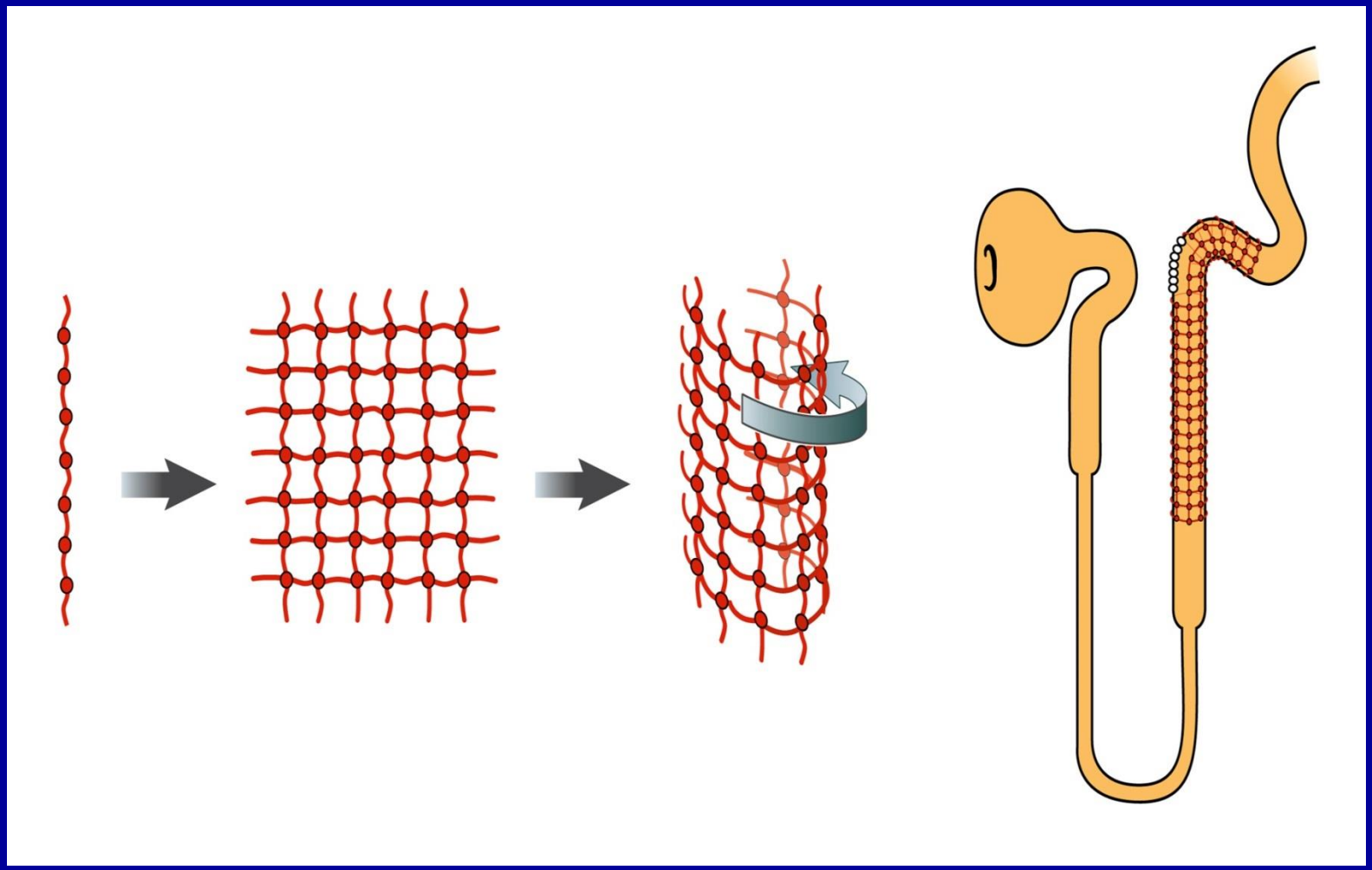
- Patients who produce less uromodulin excrete more sodium, have lower blood pressures, and have less interstitial fibrosis.

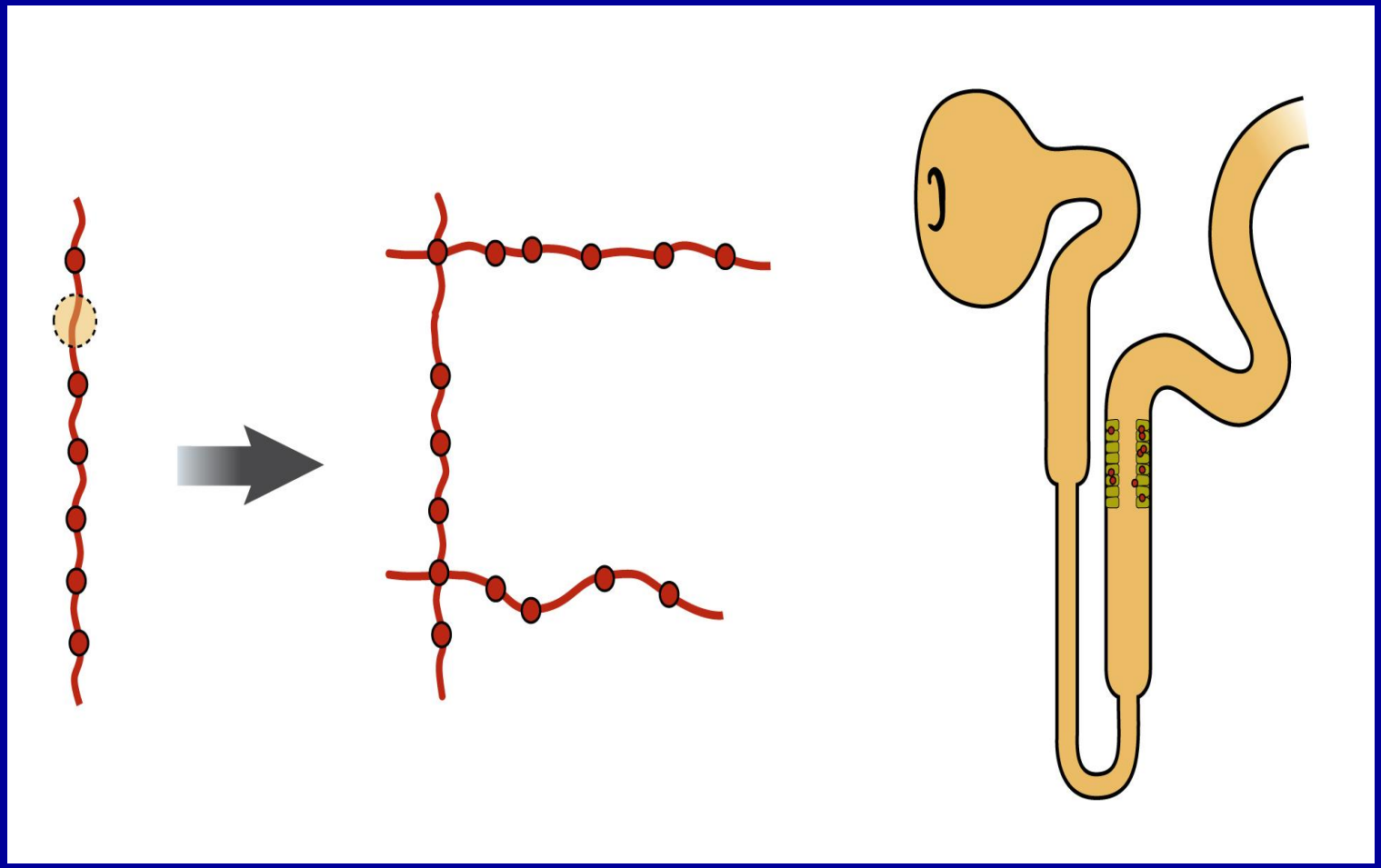
Renigunta A et al., J Biol Chem 2011
Mutig K et al. J biol Chem 2011

THP Production

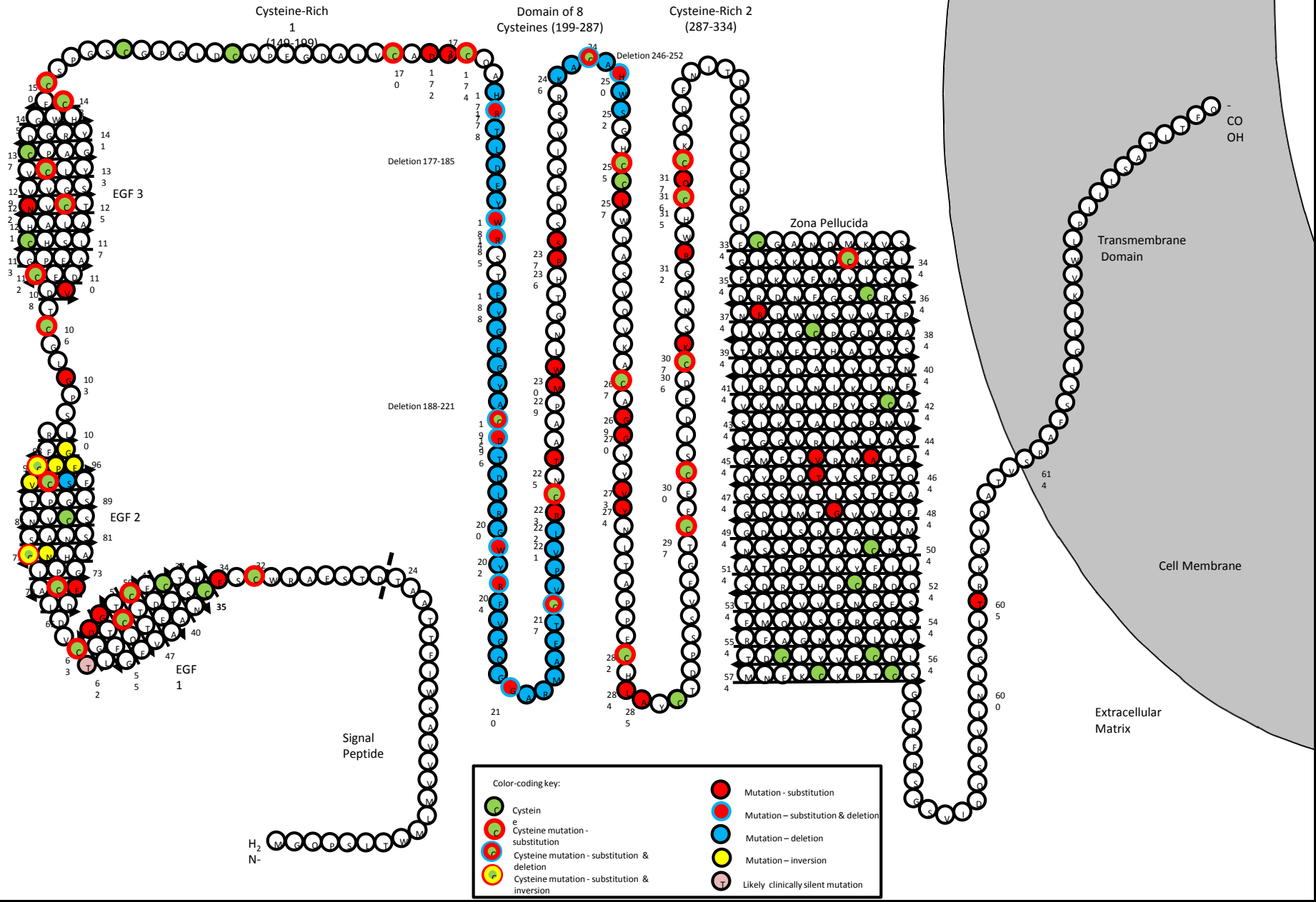
- Uromodulin has more cysteines than any other proteins in the body.
- These cysteines allow uromodulin to cross-link.
- It is critical that the correct cysteines cross linke for the function of the molecule.

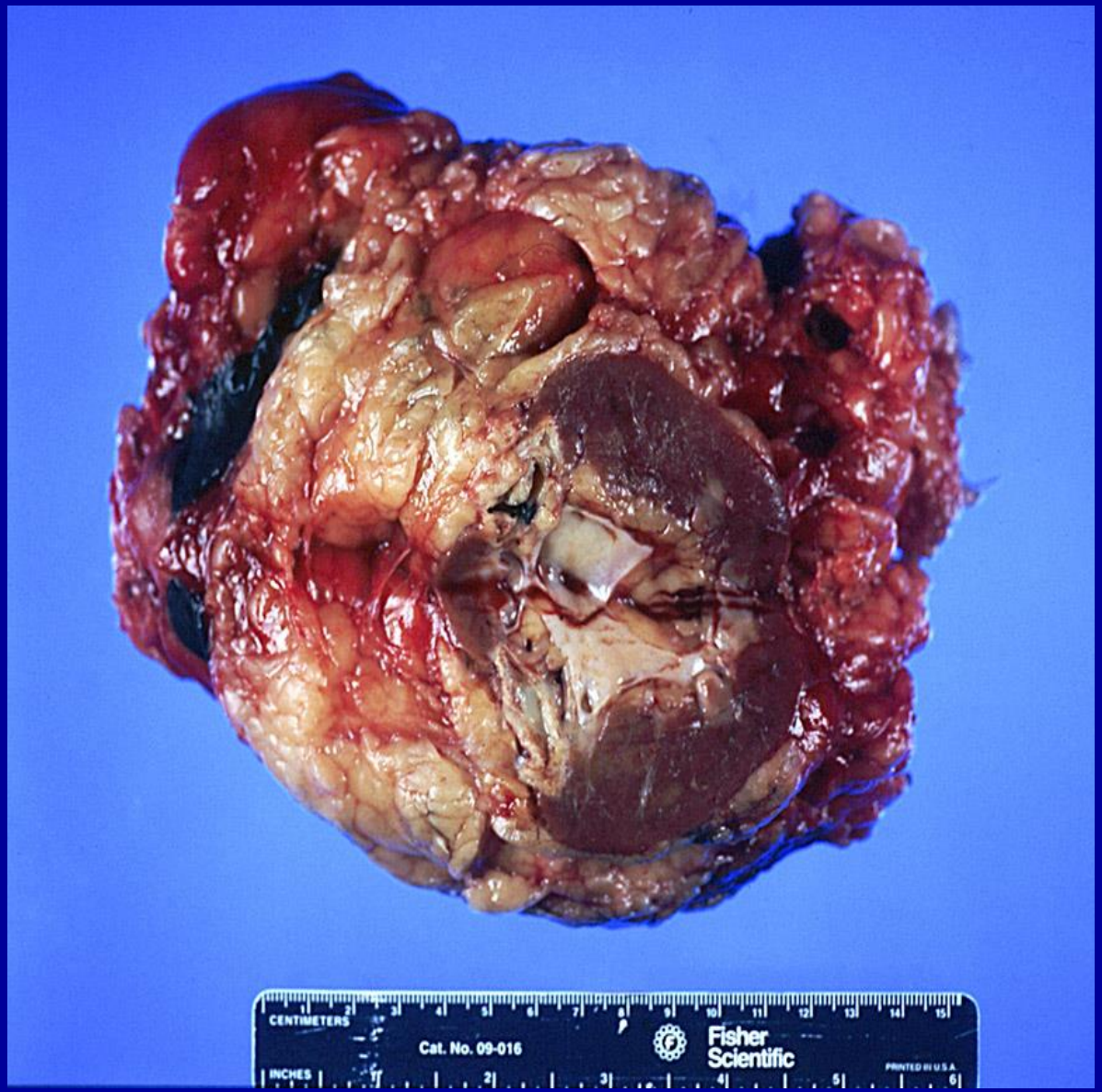
- About 75% of mutations in UKD involve a cysteine.
- Almost all are predicted to affect structure
- No mutations resulting in truncation of the protein
- The abnormal uromodulin cannot form its normal structure. It precipiates in the cell and builds up.

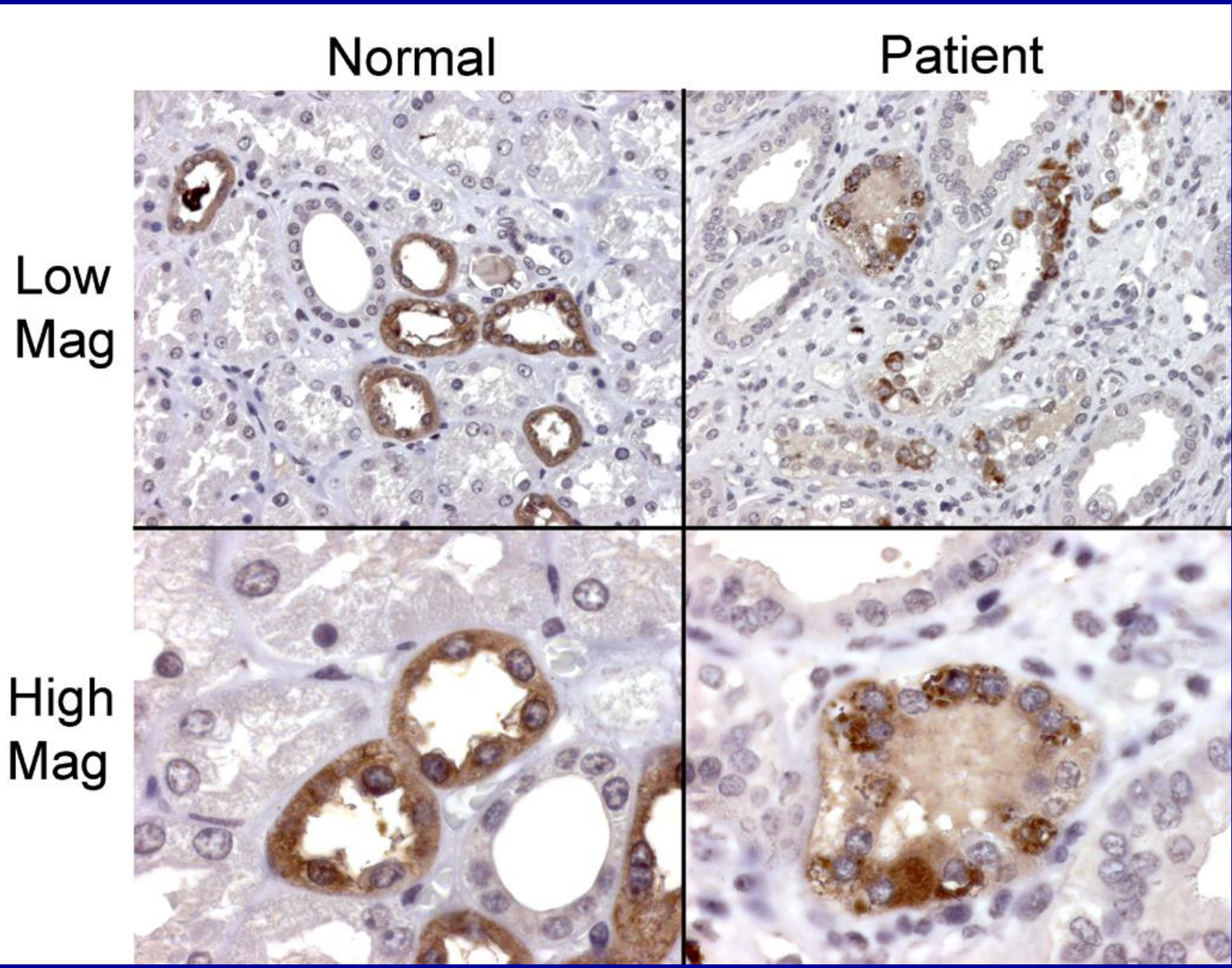


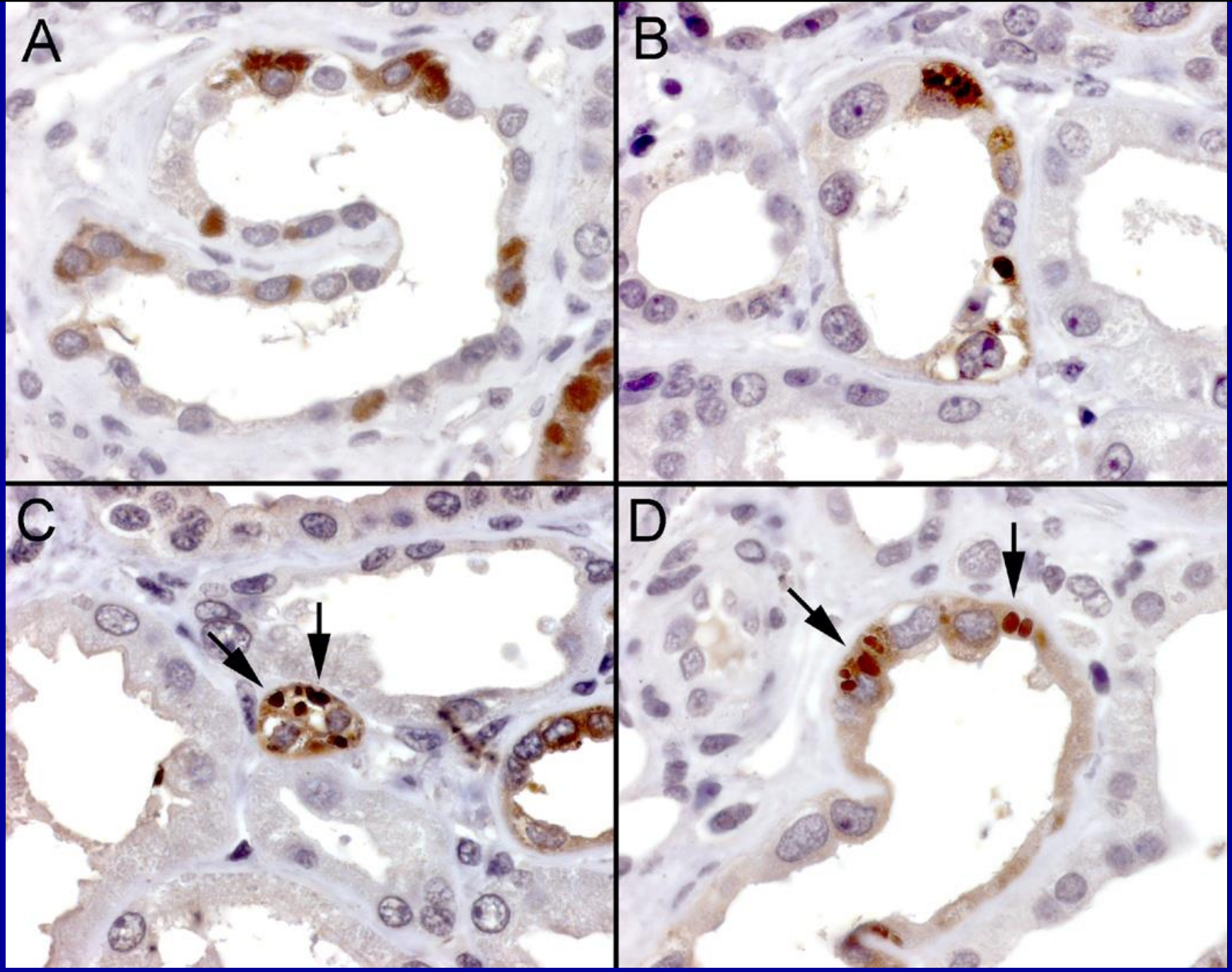


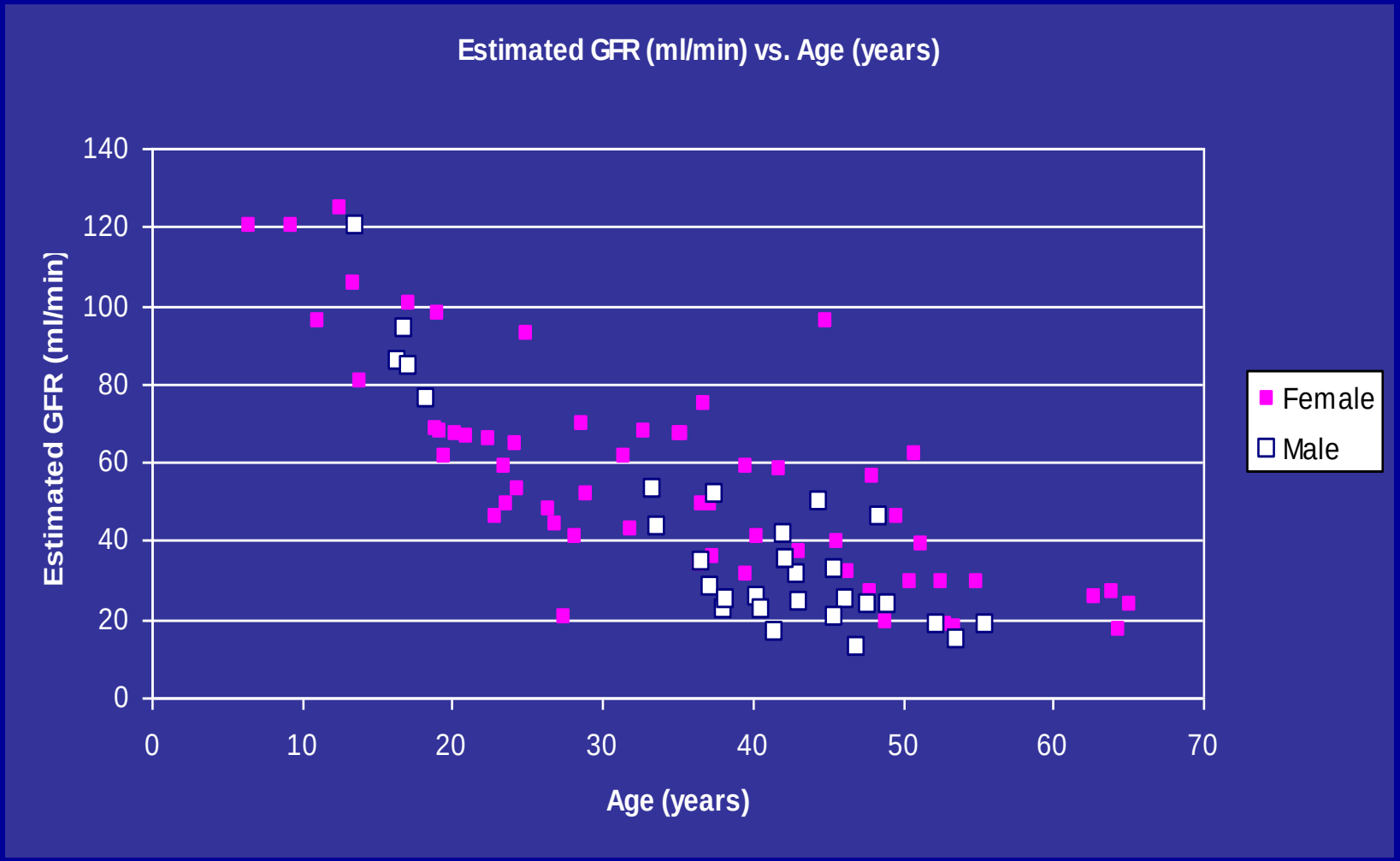
UMOD Mutations that Cause Uromodulin Kidney Disease




CENTIMETERS
INCHES
Cat. No. 09-016
Fisher Scientific
PRINTED IN U.S.A.

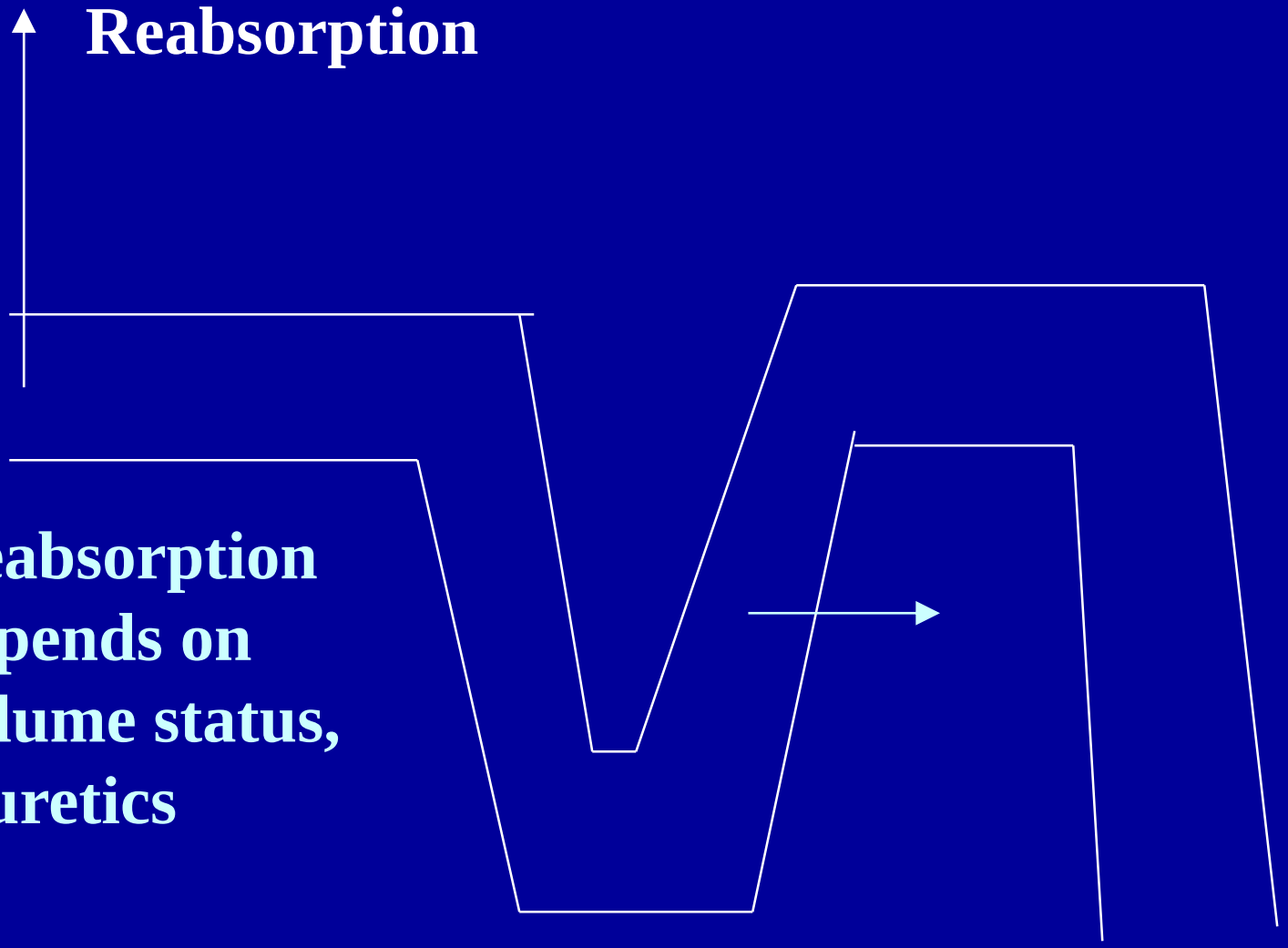

Normal
Patient
Low Mag
High Mag


A
B
C
D


Estimated GFR (ml/min) vs. Age (years)
Estimated GFR (ml/min)
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Age (years)
Female
Male

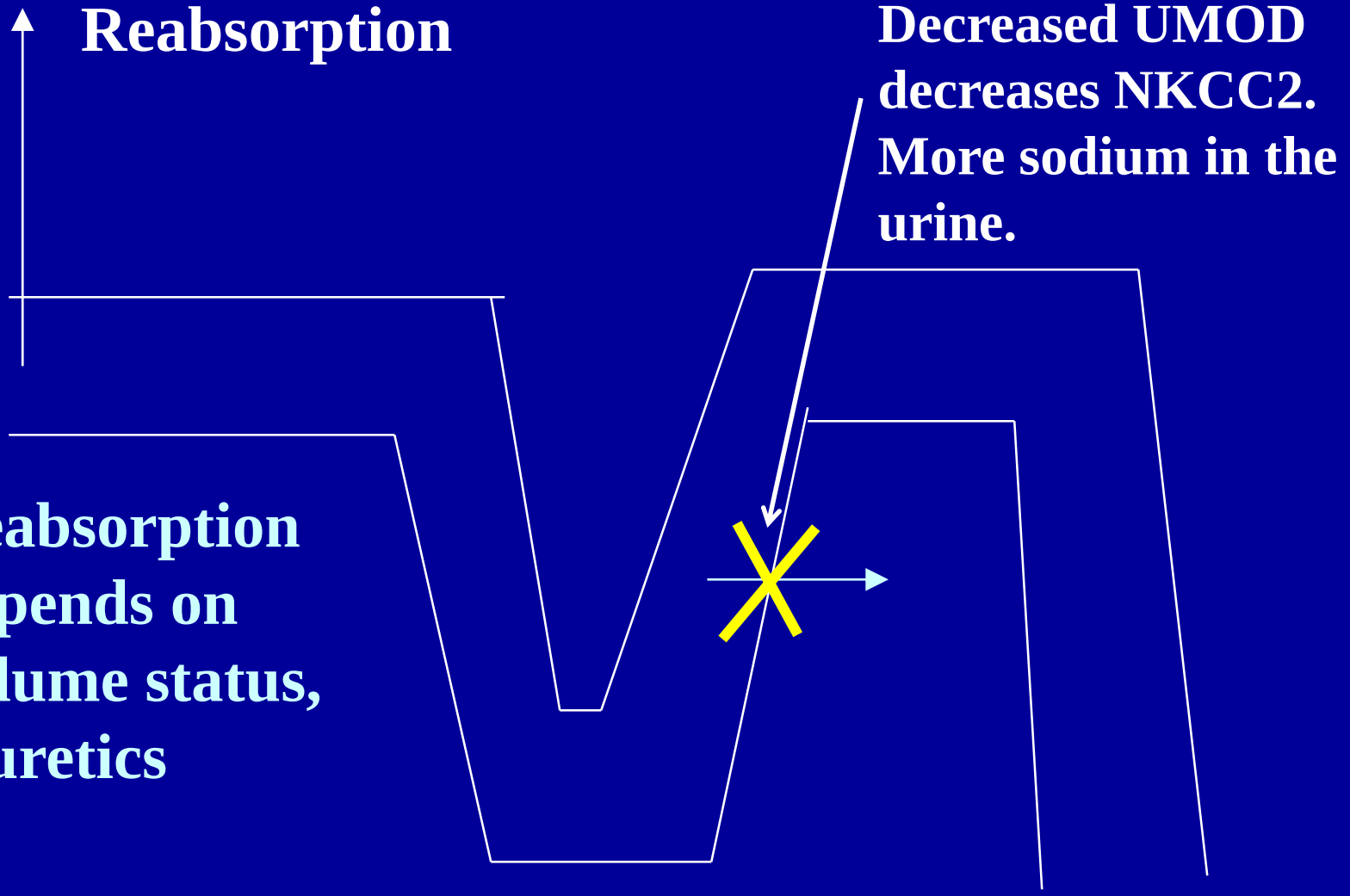
How does the uromodulin mutation cause gout?

Sodium Reabsorption



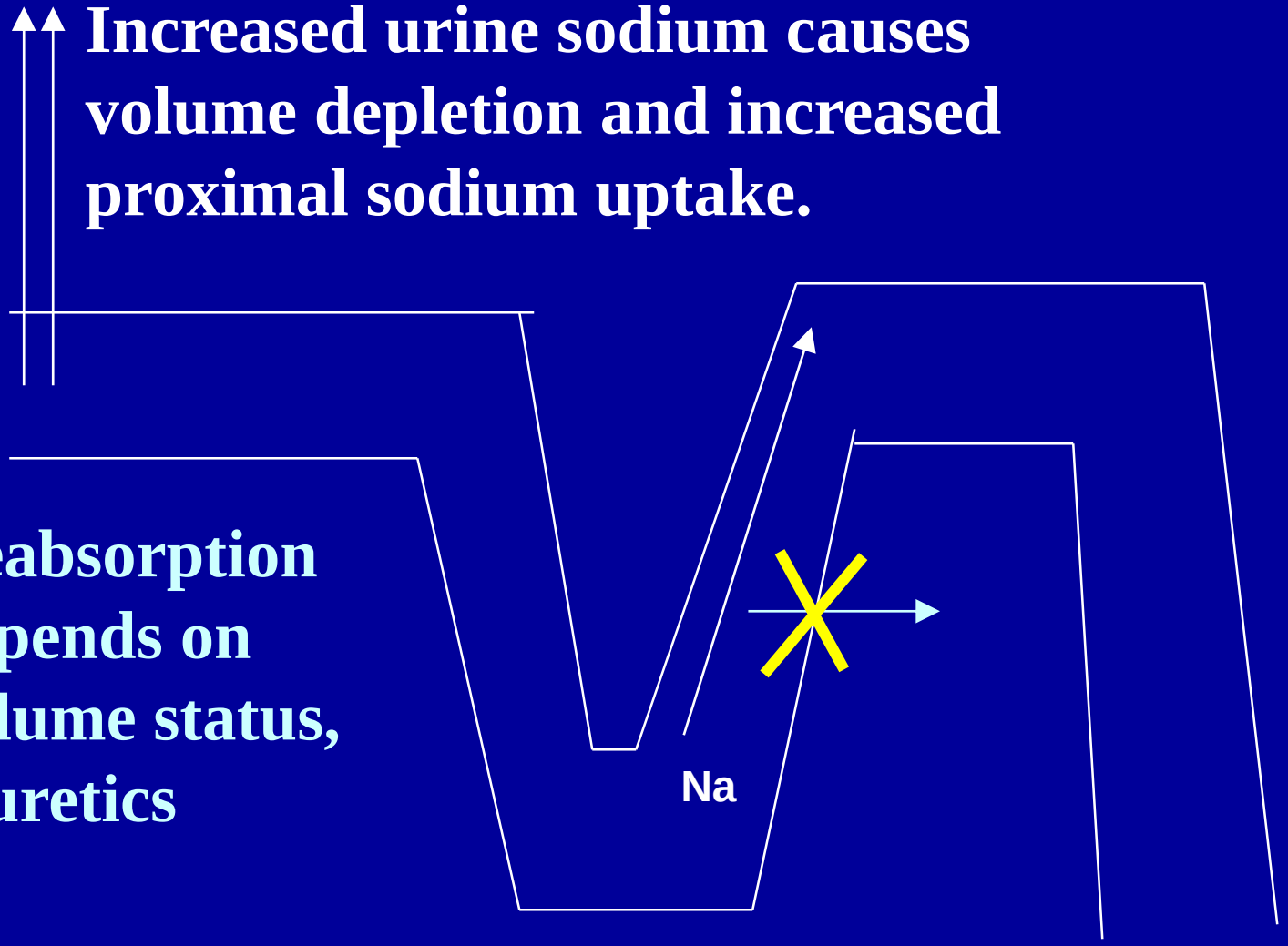
Reabsorption depends on volume status, diuretics

Sodium Reabsorption in UMOD mutation



Sodium Reabsorption

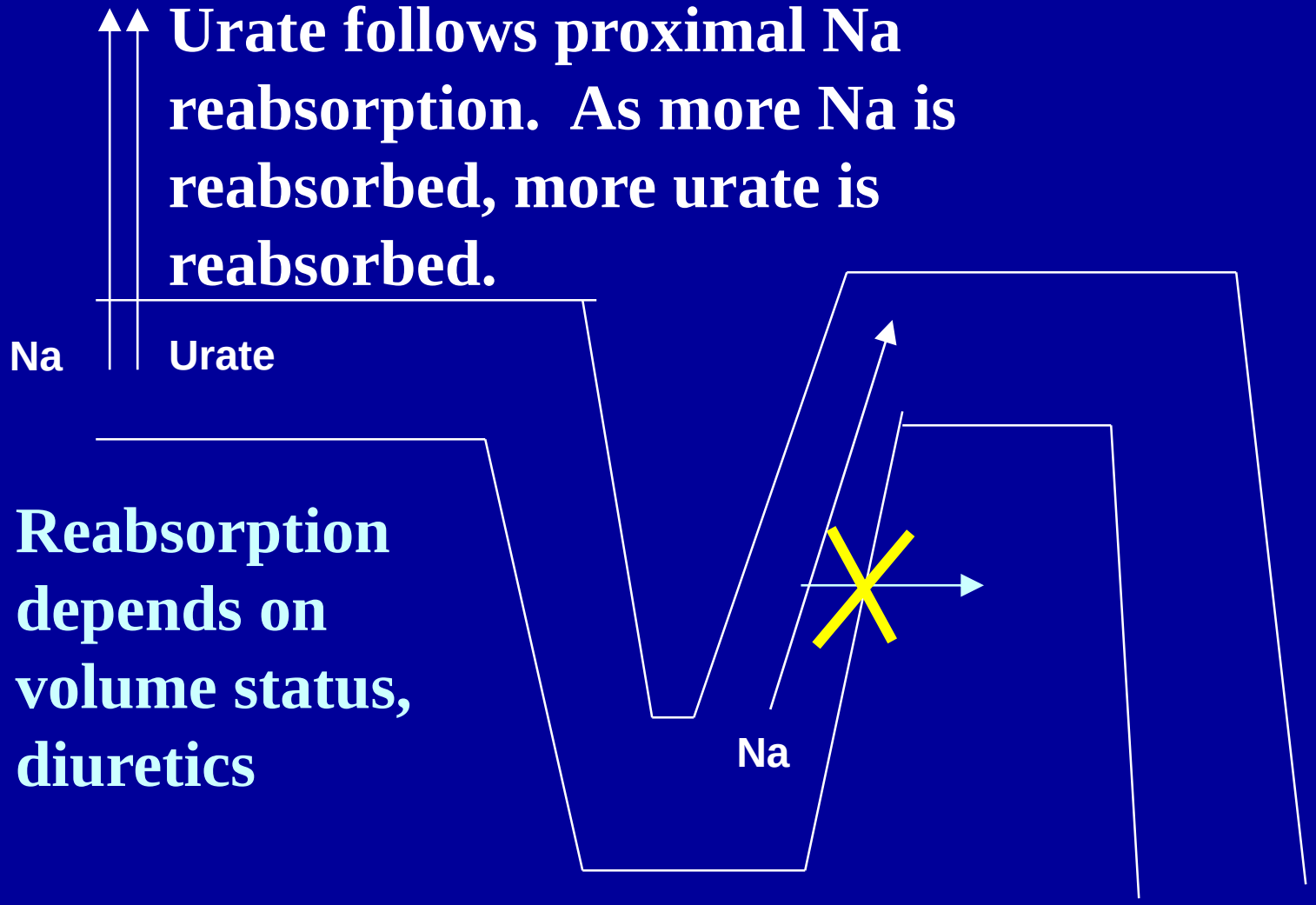
Increased urine sodium causes volume depletion and increased proximal sodium uptake.



Reabsorption depends on volume status, diuretics

Urate Reabsorption

Urate follows proximal Na reabsorption. As more Na is reabsorbed, more urate is reabsorbed.



Reabsorption depends on volume status, diuretics

- Hyperuricemia and gout.

- More sodium is reabsorbed proximally.
- More urate is reabsorbed proximally.
- Hypouricosuric hyperuricemia

Diagnosis

- Suspect disease based on cardinal manifestations
- Send sample for UMOD genetic analysis
- We can aid in the diagnosis of new cases.

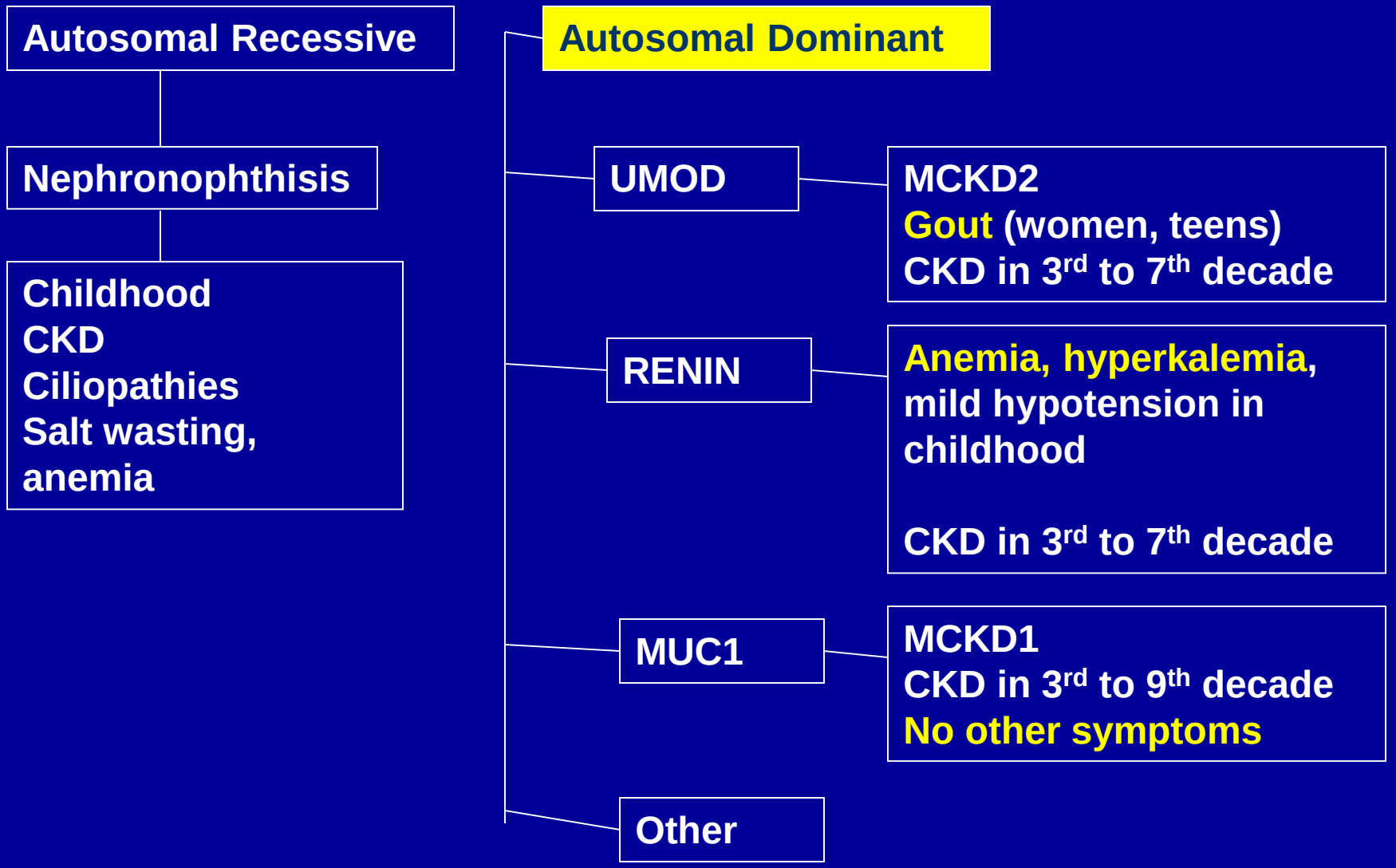
Treatment

- Allopurinol is effective in the treatment of gout and MAY slow progression of kidney disease.
- Otherwise treatment is supportive.
- Patient should undergo pre-emptive kidney transplantation.

Mutation	UMOD	REN	MUC-1
Loss of normal gene function	↑Urate Gout		
Tx of loss of fxn	Allopurinol		
Knockout mouse	No effect		
Gene deletion or truncation	No effect		
Abnormal production	Intracellular deposition, Kidney failure		

- 8 year old girl
- Anemia at 1 year testing
- Mild hypotension
- Serum potassium mildly elevated
- Acute kidney injury when given a non-steroidal medication for a febrile illness.
- Father and granfather also with anemia in childhood and kidney failure

Inherited Interstitial Kidney Disease



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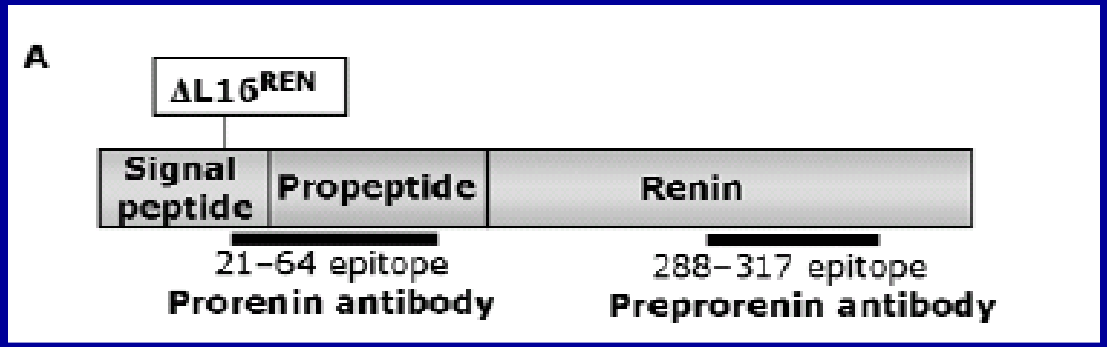


- Decreased production of normal renin
- Deposition of abnormal renin intracellularly

Effects of Low Renin

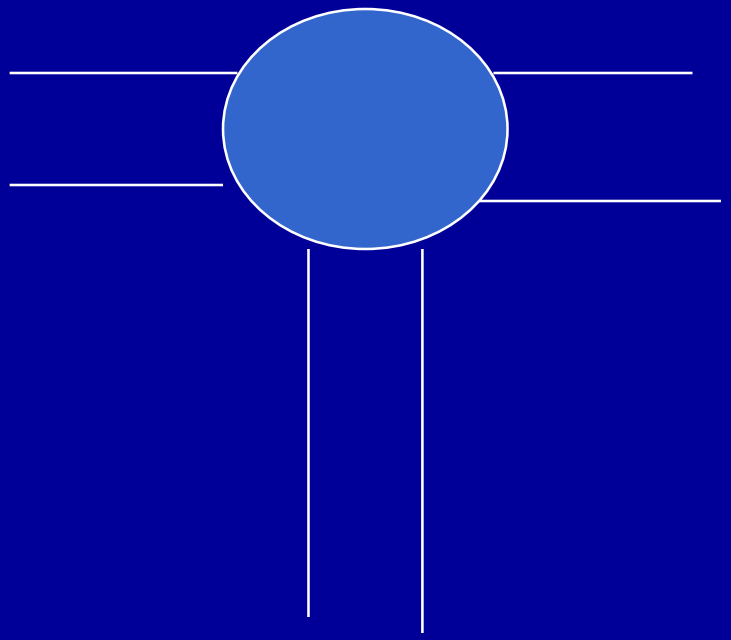
- Low BP
- High normal potassium
- Anemia
- Predisposition to acute kidney injury

Anemia

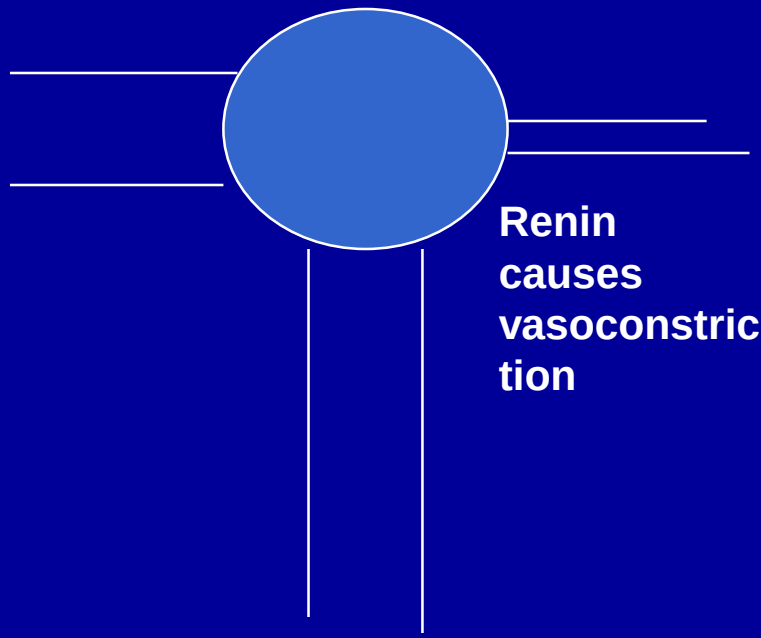
- Low erythropoietin levels
- Due to decreased renin production
  - Similar to ACE inhibitor in ESRD
  - Polycythemia in kidney transplantation

- Present by 1 year of age
- Found in all affected individuals
- Hgb from 8 to 10 g/dl.
- Responds to erythropoietin
- Resolves by adolescence due to sex steroid production

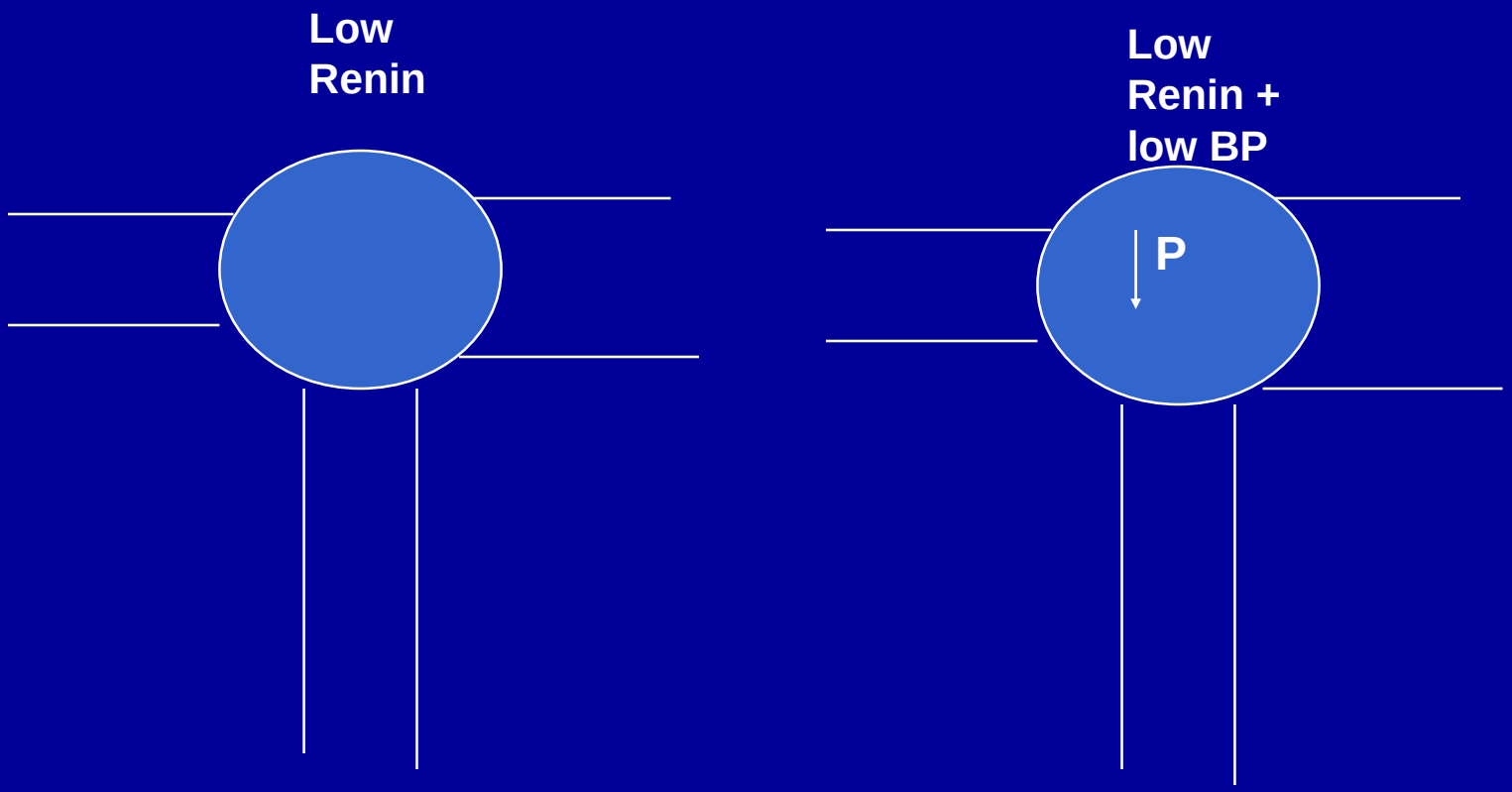
Normal BP



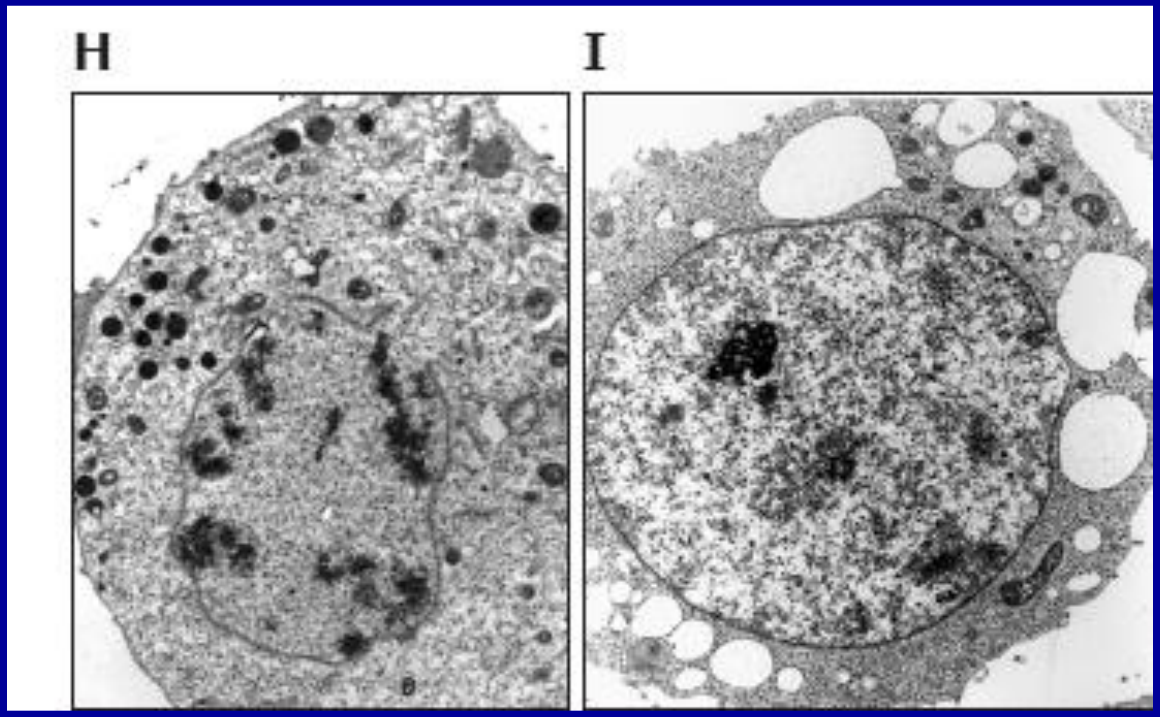
Low BP



Renin causes vasoconstriction



8 year old child with fever, nausea, headache – given ibuprofen
This constellation will lead to AKI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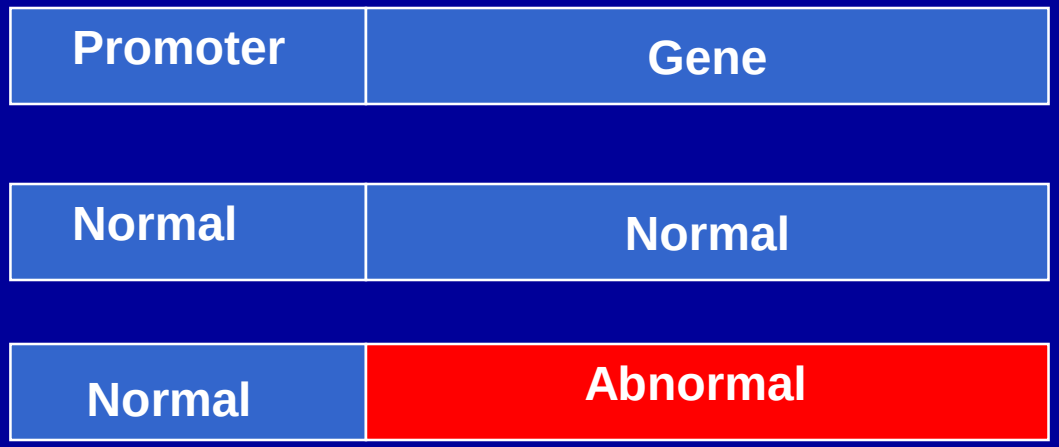
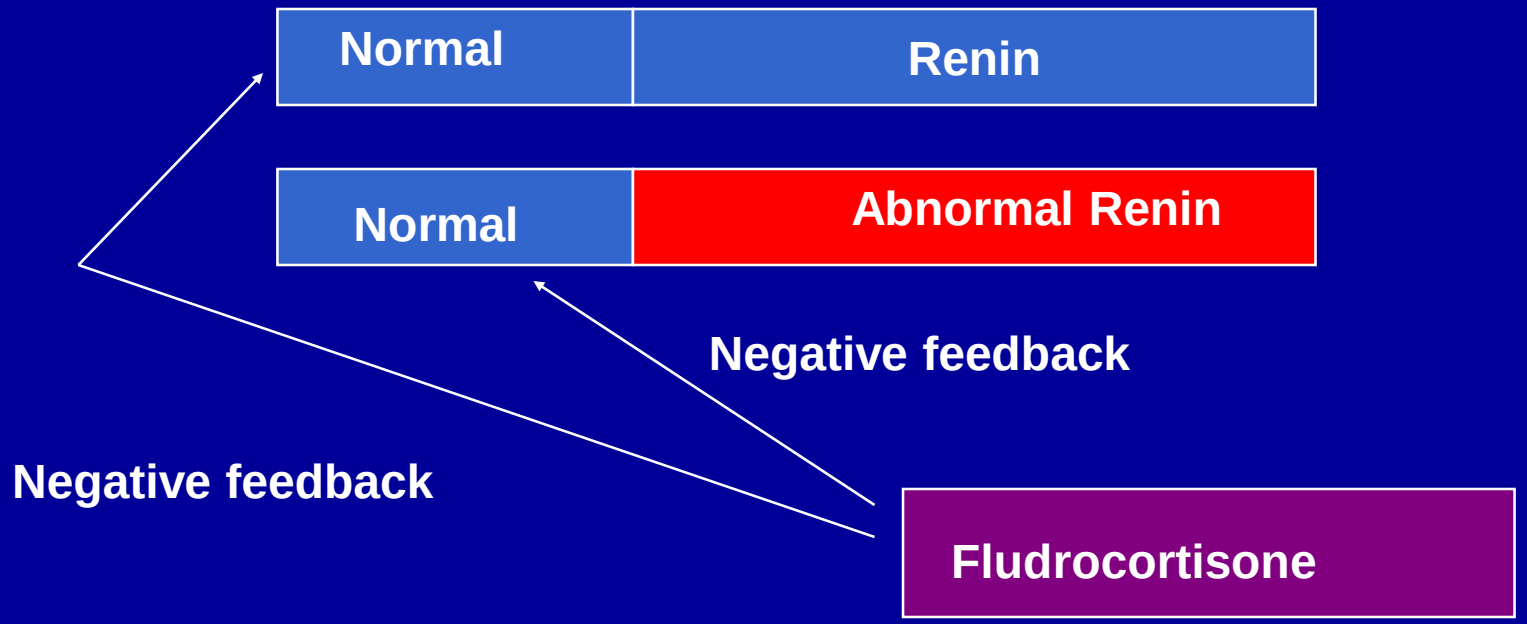
I



We want to decrease production via the promoter, but this will result in decreased production of both alleles.


Normal
Renin
Normal
Abnormal Renin
Negative feedback
Negative feedback
Fludrocortisone

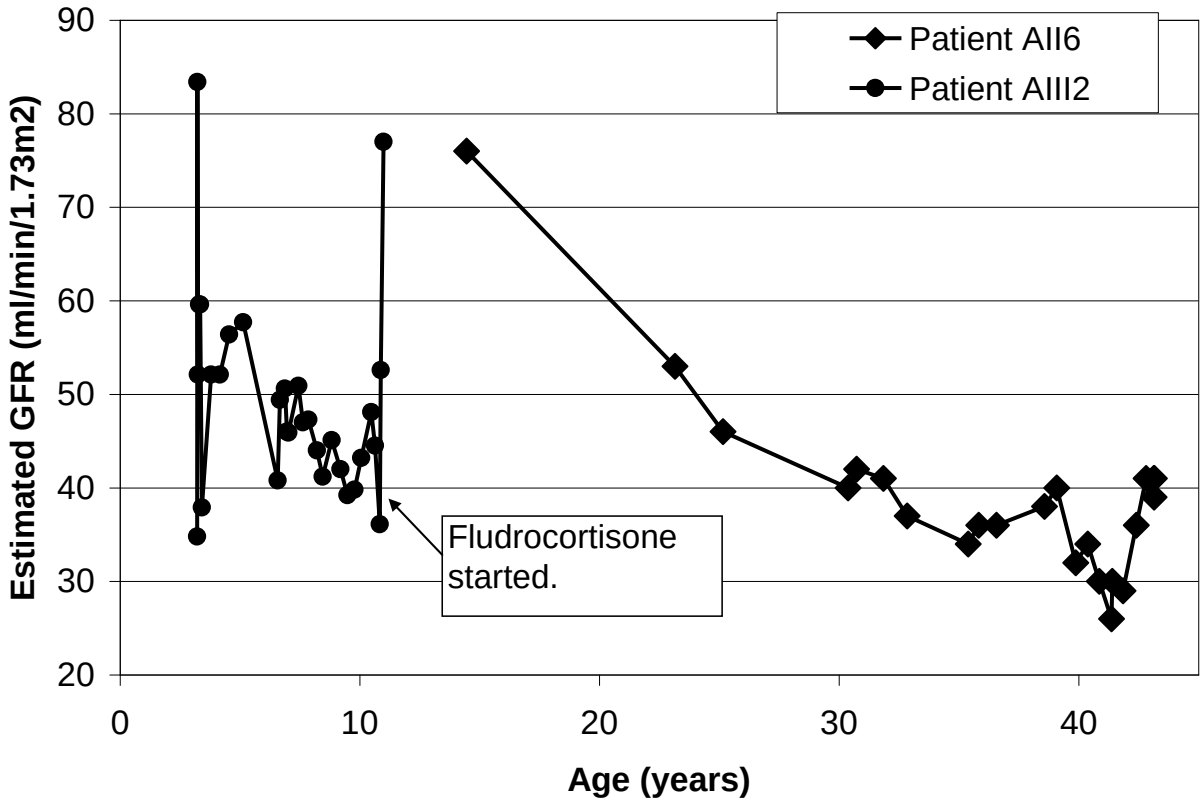
Fludrocortisone Treatment

- Treats aldosterone deficiency
  - Corrects mild hyperkalemia
  - Decreases risk from volume depletion
- Removes “bad” renin
  - Prevents tubulo-interstitial fibrosis

Fludrocortisone Treatment

Time	BP	Wt	K	Cr	Uvol
-11wk	87/50		5.0	114	1825
-1wk		39.8	5.6	140	2275
1wk	106/69	40.9	4.2	96	2450
6wks	112/67		4.3	88	2675

Figure 2. Estimated Glomerular Filtration Rate vs. Age(Years)



Mutation	UMOD	REN	MUC 1
Loss of normal gene function	↑Urate Gout	↓BP, Hgb ↑K, Urate	
Tx of loss of fxn	Allopurinol	Fludrocortisone	
Knockout mouse	No effect	Death in utero	
Gene deletion or truncation	No effect	No effect for one gene	
Abnormal production	Intracellular deposition, Kidney failure	Intracellular deposition, Kidney failure	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HIGHEST PEAK EAST OF THE MISSISSIPPI RIVER
VENUS FLY TRAP
USS NORTH


SR
1003
CHICKEN
RD
REVA
RD

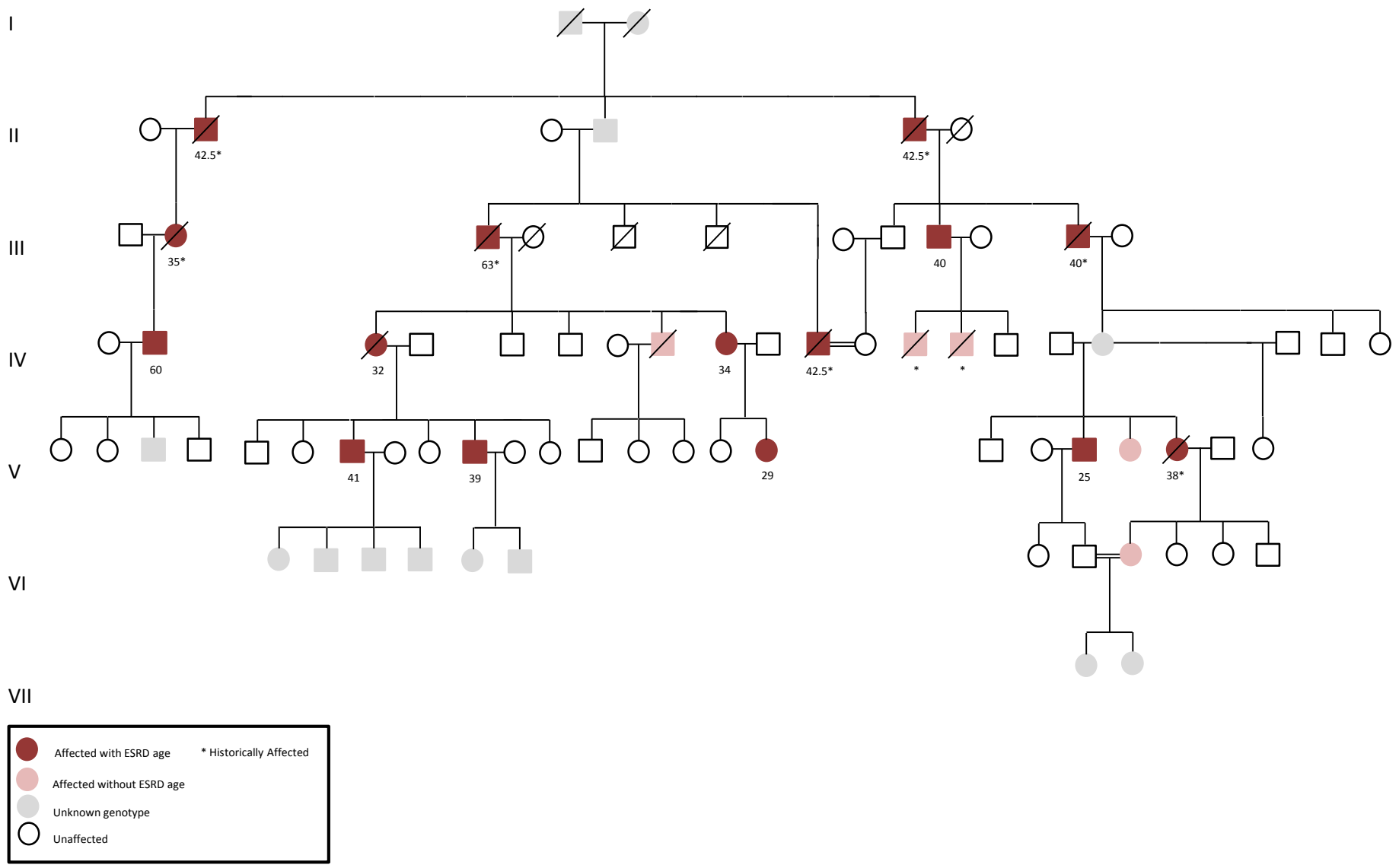
Case Description

- 35 year old white female presents for evaluation of serum creatinine 200 mmol/l
- The patient developed HTN (140/90) at age 34 which has been easily treated with enalapril, 20 mg po q d.
- There is no history of anemia, hyperkalemia, or gout
- PE: Unremarkable

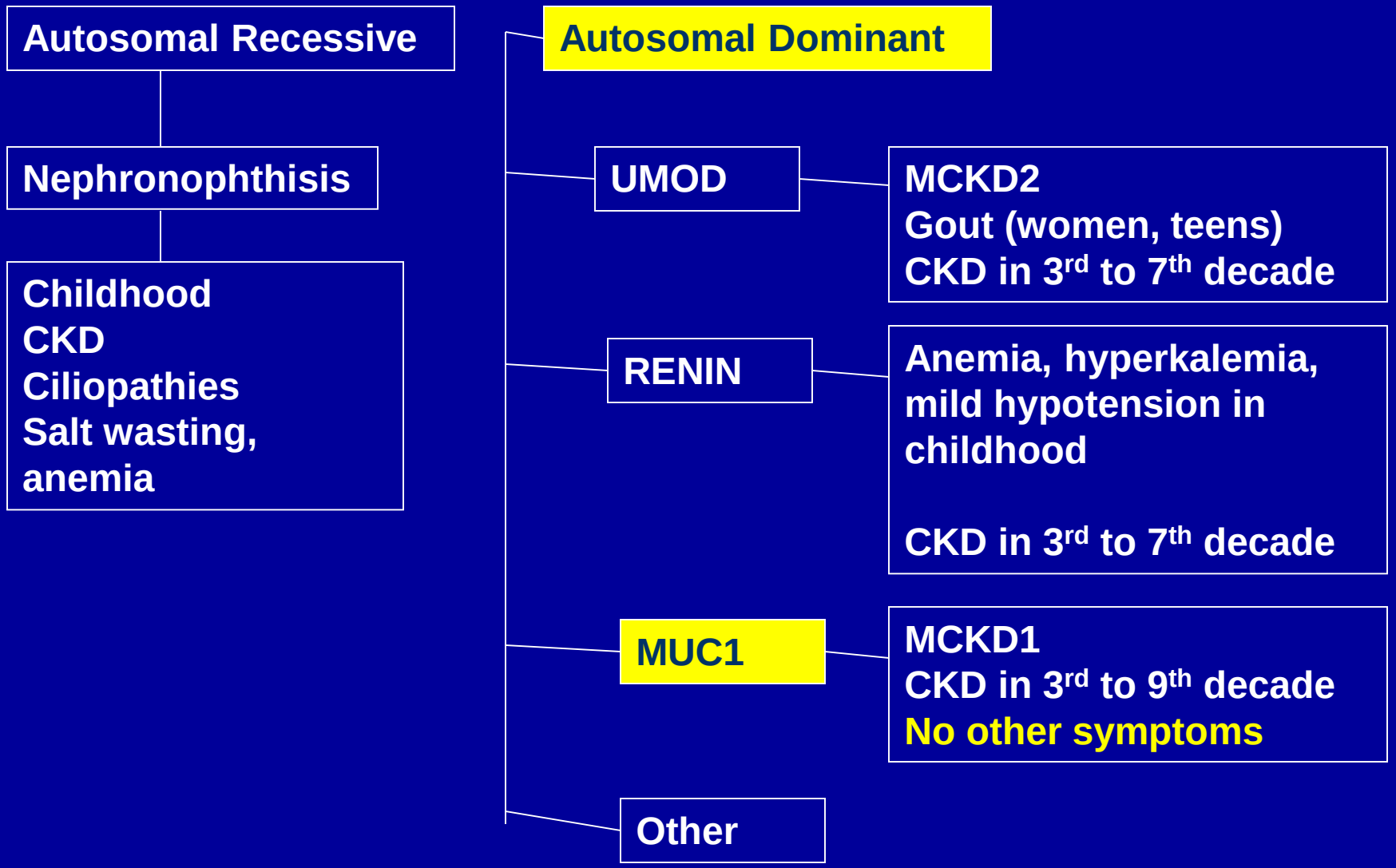
Case Description

- Urinalysis: Bland without blood or protein
- Renal ultrasound: Normal sized kidneys, no cysts

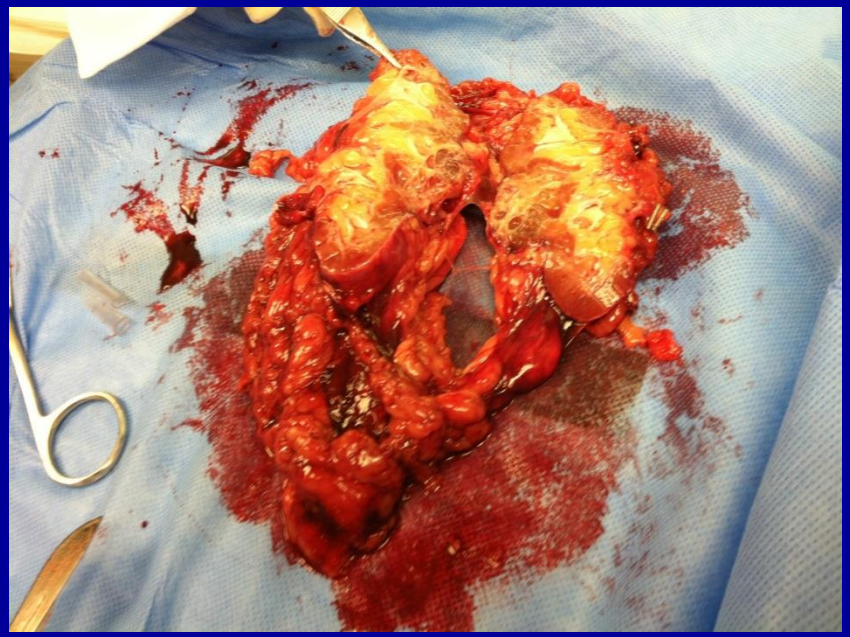
Family L1

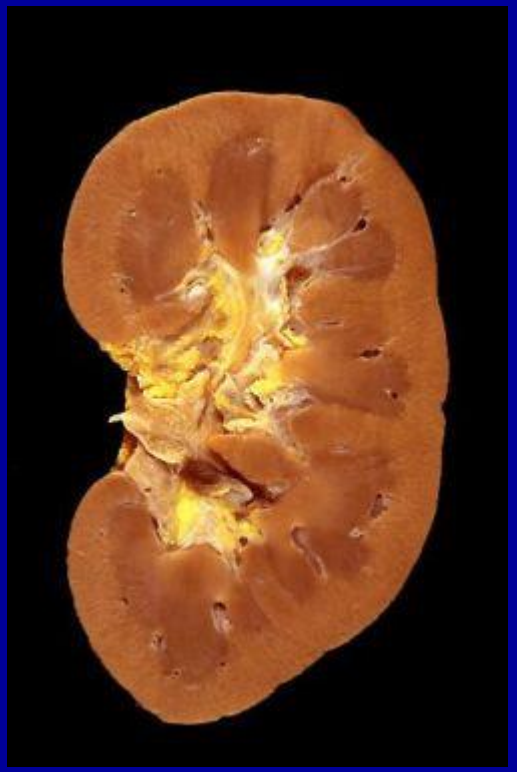

I
II
III
IV
V
VI
VII
42.5*
42.5*
35*
63*
40
40*
60
32
34
42.5*
*
*
41
39
29
25
38*
Affected with ESRD age
* Historically Affected
Affected without ESRD age
Unknown genotype
Unaffected

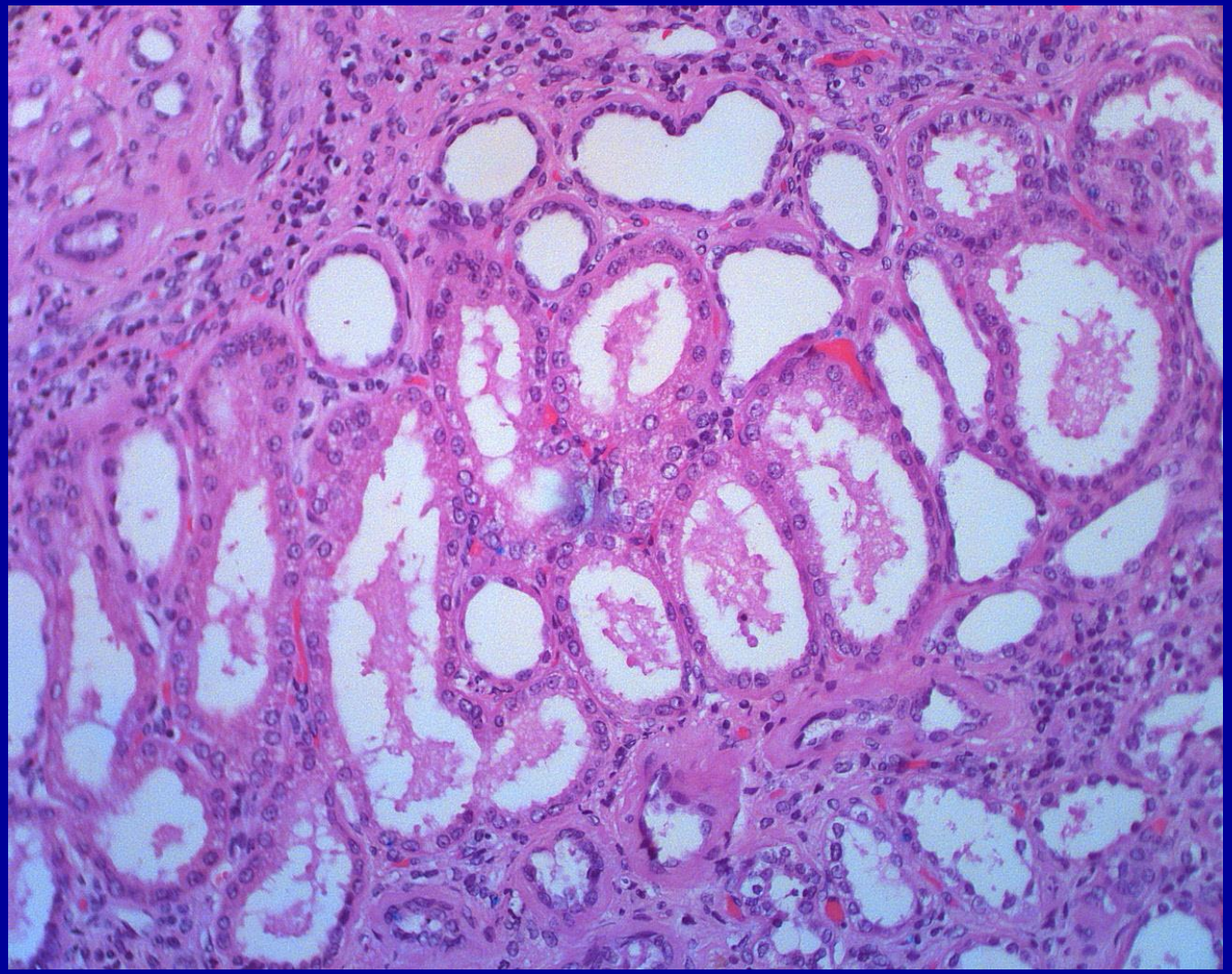
Inherited Interstitial Kidney Disease



Pathology







Medullary Cystic Kidney Disease Type 1

- Autosomal dominant
- Slowly progressive chronic kidney disease

Linkage

- First performed by Otto, Hildebrandt in 2001
- Subsequently performed by other groups
- Consistent linkage to Chromosome 1
- 37 genes evaluated with mutational analysis

MCKD1 genetics team

Linkage, sequence analysis

Andrew Kirby
Christine Stevens
Kiran Garimella
Mark dePristo
Jim Robinson

Bioinformatics Analysis
Jimmie Ye
Nathalie Pochet
Aviv Regev
Lizzy Rossin

MUC1, targeted sequence & assembly

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Dave Jaffe
Chad Nusbaum

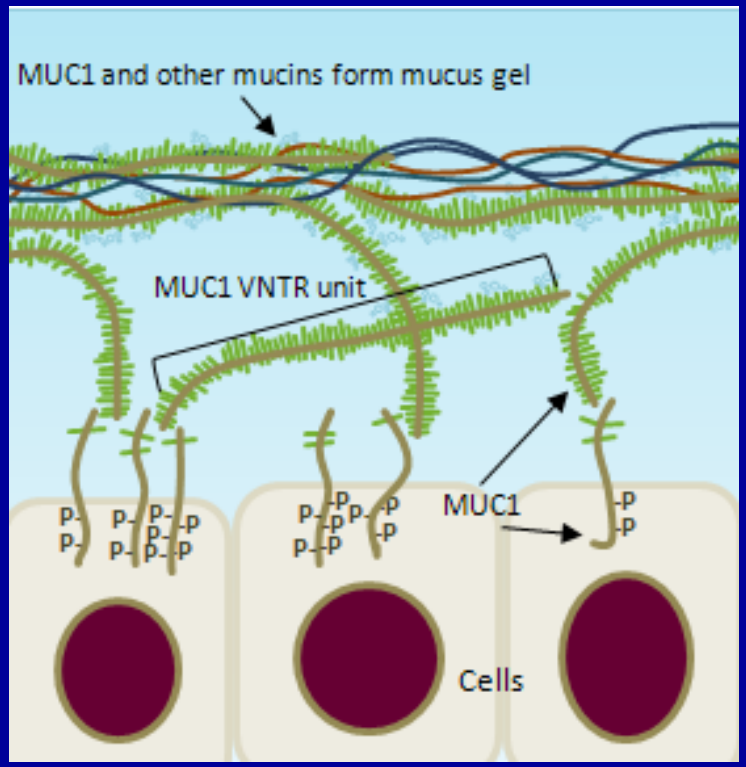
DNA sequencing
Jen Baldwin
Jane Wilkinson
Lauren Ambrogio
Snaevar Sigurdsson
Kerstin Lindblad-Toh

Clinical Phenotyping & Functional Insights

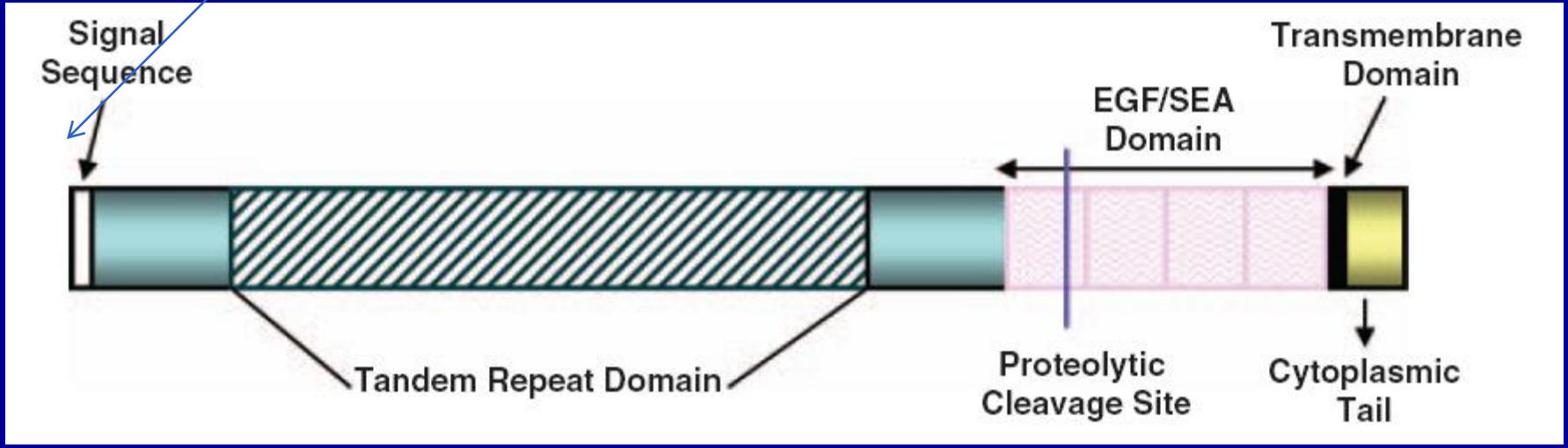
Tony Bleyer
Suzanne Hart

MUC1

- MUC1 is a membrane-anchored mucoprotein
- Expressed in secretory epithelium of the lungs, kidneys, breasts, GI tract.
- Contains a VNTR unit for glycosylation



Amino terminus



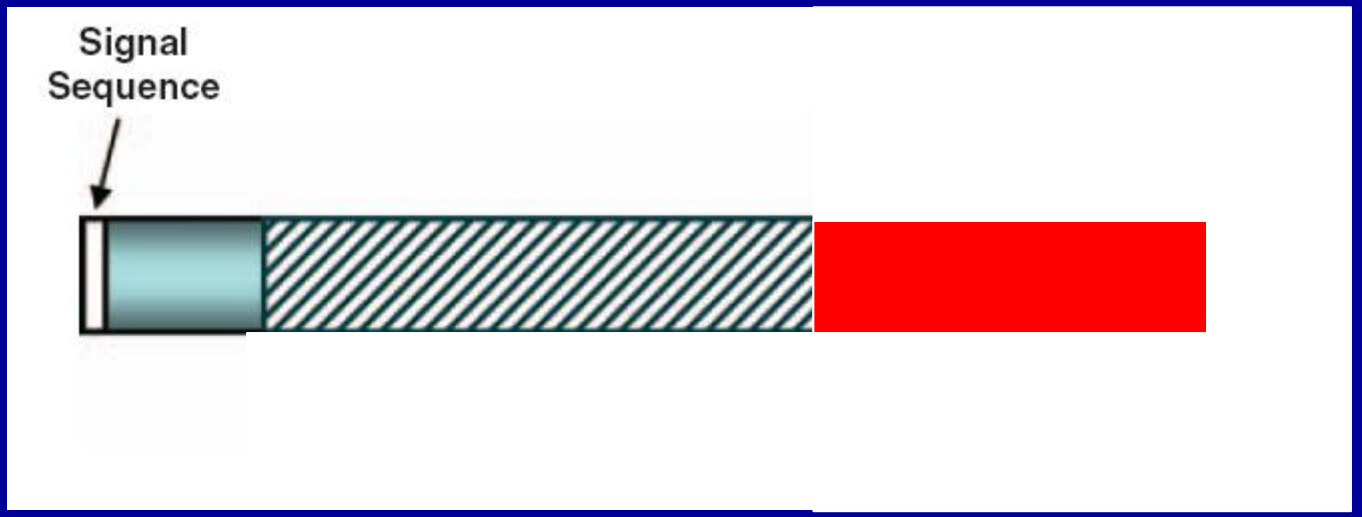
Extra C in Patient OK #563 Causes Frameshift

V	T	S	A	P	D	T	R	P	A	P	G	S	T	A	P	P	S	P	R
C	H	L	G	P	G	H	Q	A	G	P	G	L	H	R	P	P	S	P	R
C	H	L	G	P	G	H	Q	A	G	P	G	L	H	R	P	P	S	P	R
C	H	L	G	P	G	H	Q	A	R	P	G	L	H	R	P	P	S	P	R
C	H	L	G	P	G	H	Q	A	G	P	G	L	H	R	P	P	S	P	R
C	H	L	G	P	G	E	Q	A	G	P	G	L	H	R	A	R	S	P	R
C	H	L	G	P	G	E	Q	A	G	P	G	L	H	R	A	R	S	P	R
C	H	L	G	P	G	E	Q	A	G	P	G	L	H	R	A	R	S	P	R
C	H	L	G	P	G	E	Q	A	G	P	G	L	H	R	A	R	S	P	R
C	H	L	G	P	G	E	Q	A	G	P	G	L	H	R	P	P	S	P	R

MUC1 Mutation

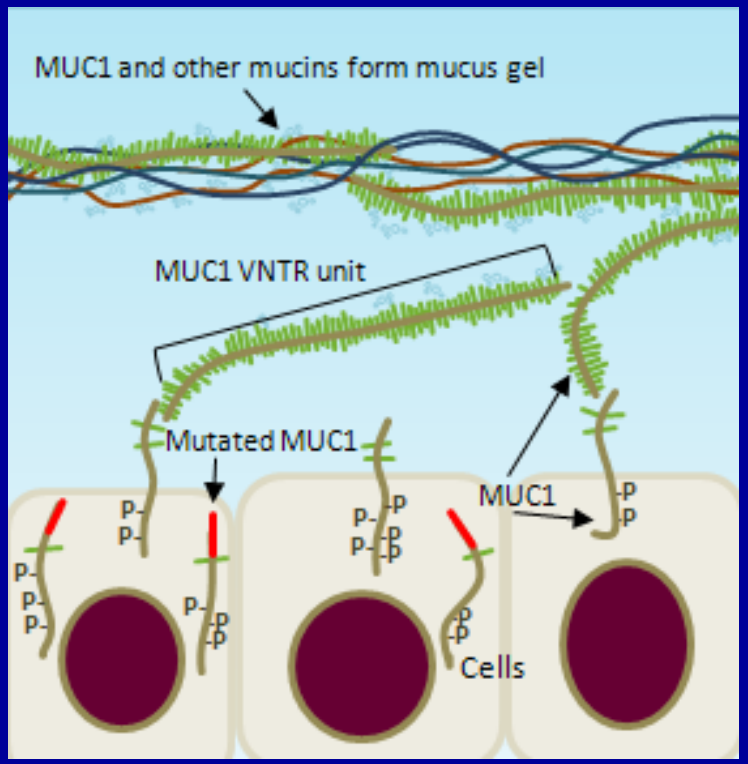
- Results in addition of a cytosine to 7 cytosines
- Creation of a new repetitive unit that repeats a unique number of times for each family
- Self termination
- Cytosolic unit is not created

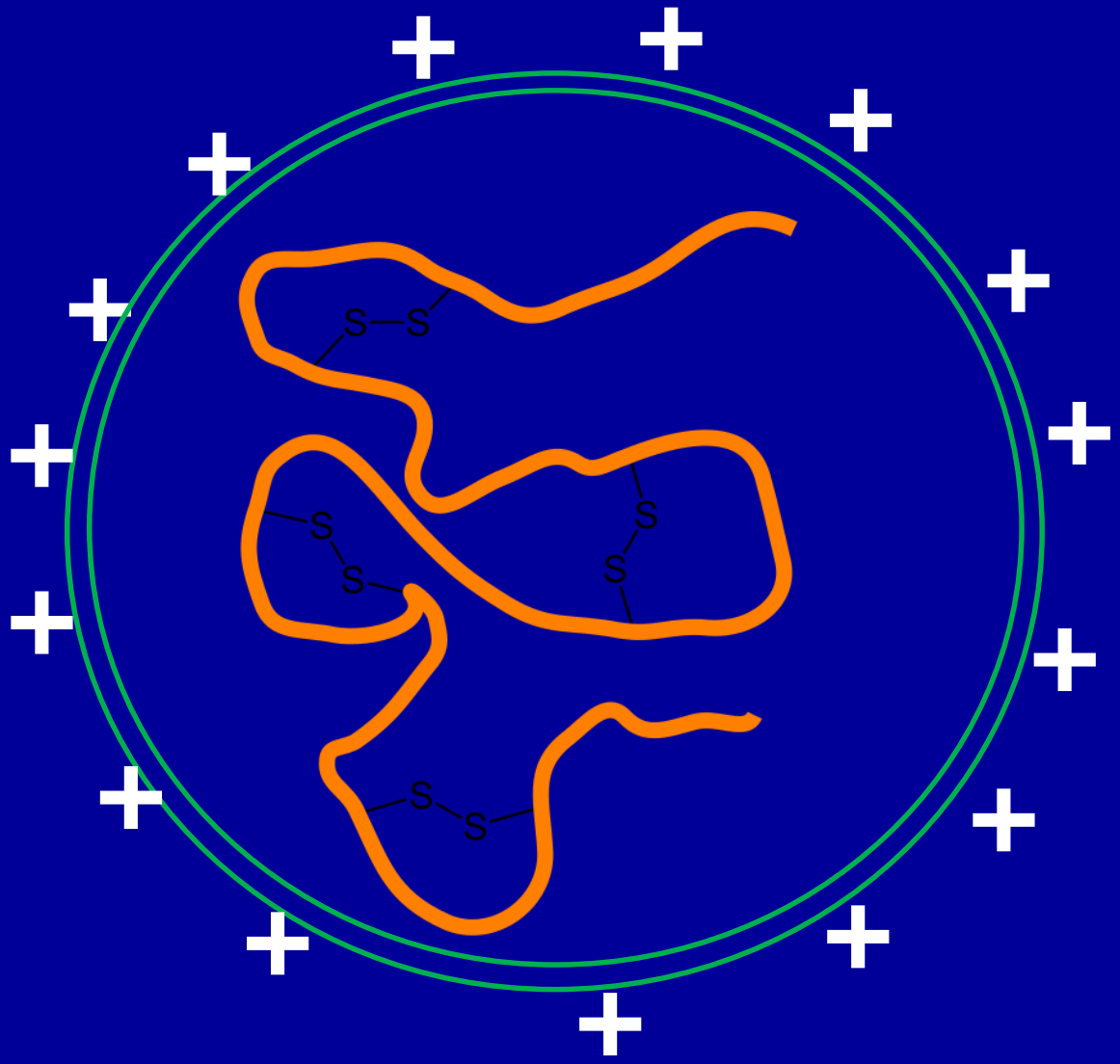
Mutant MUC1 protein



Theoretical Affect of MUC1 insertion

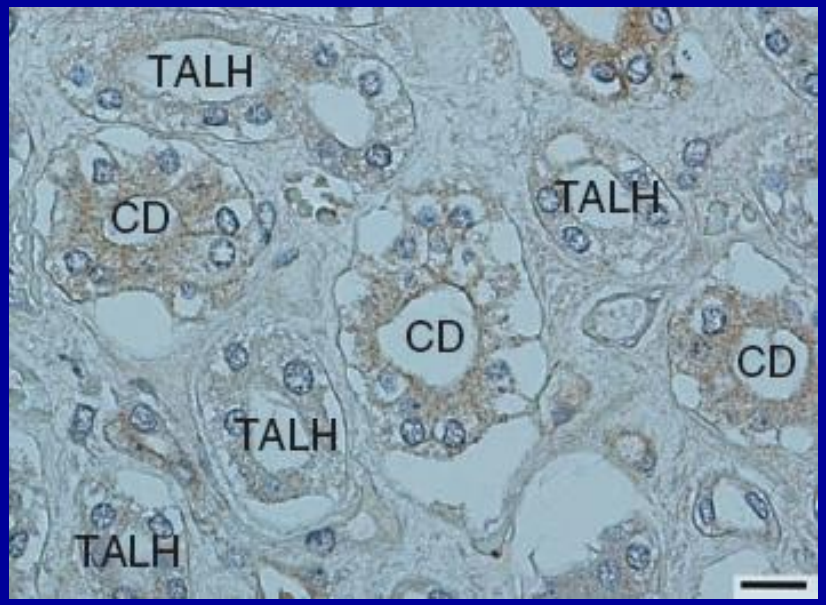
- Mutation is in the VNTR unit
- Causes a frameshift, resulting in VNTR truncation and creation of a neopeptide
- Neopeptide appears to be improperly processed in the cytoplasm
- Leads to apoptosis and slow, progressive tubular cell death

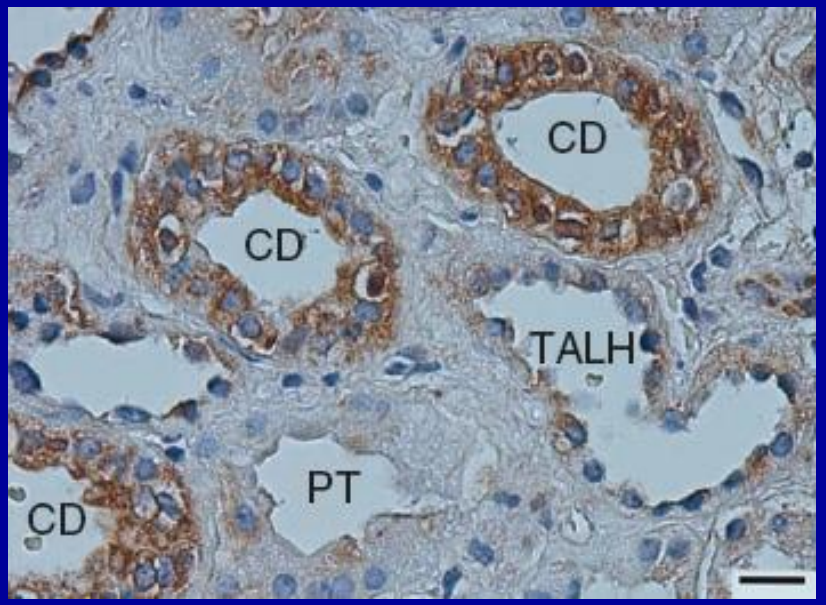




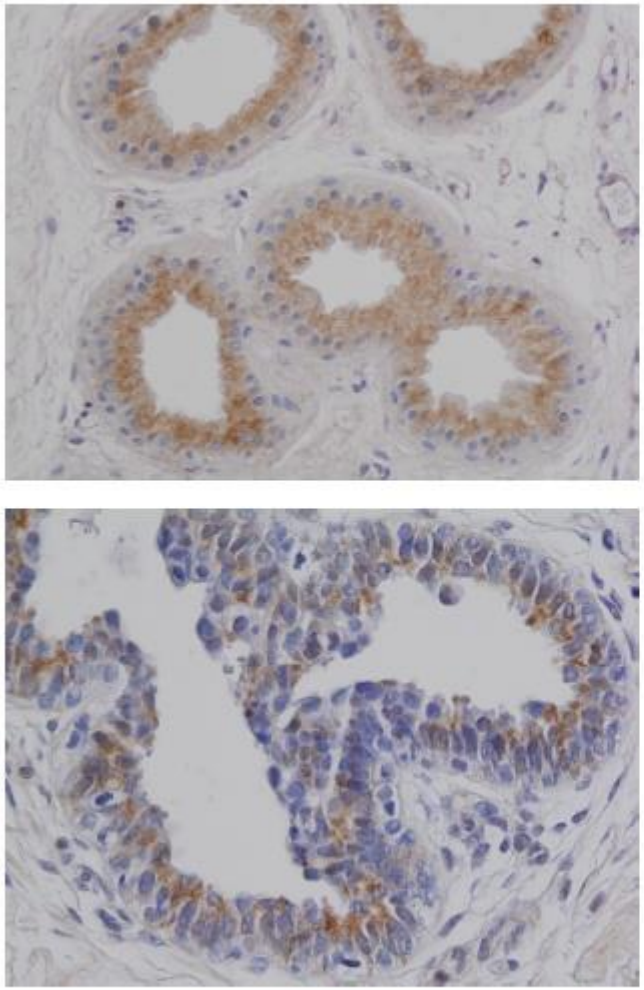
Dr. Stan Kmoch, Charles Medical School,

Normal and Mutant MUC1 Immunostaining



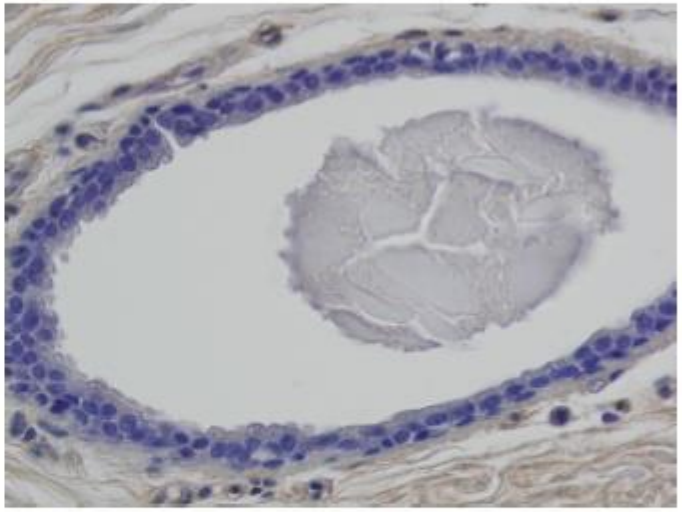


Mutant MUC1 and Breast Tissue

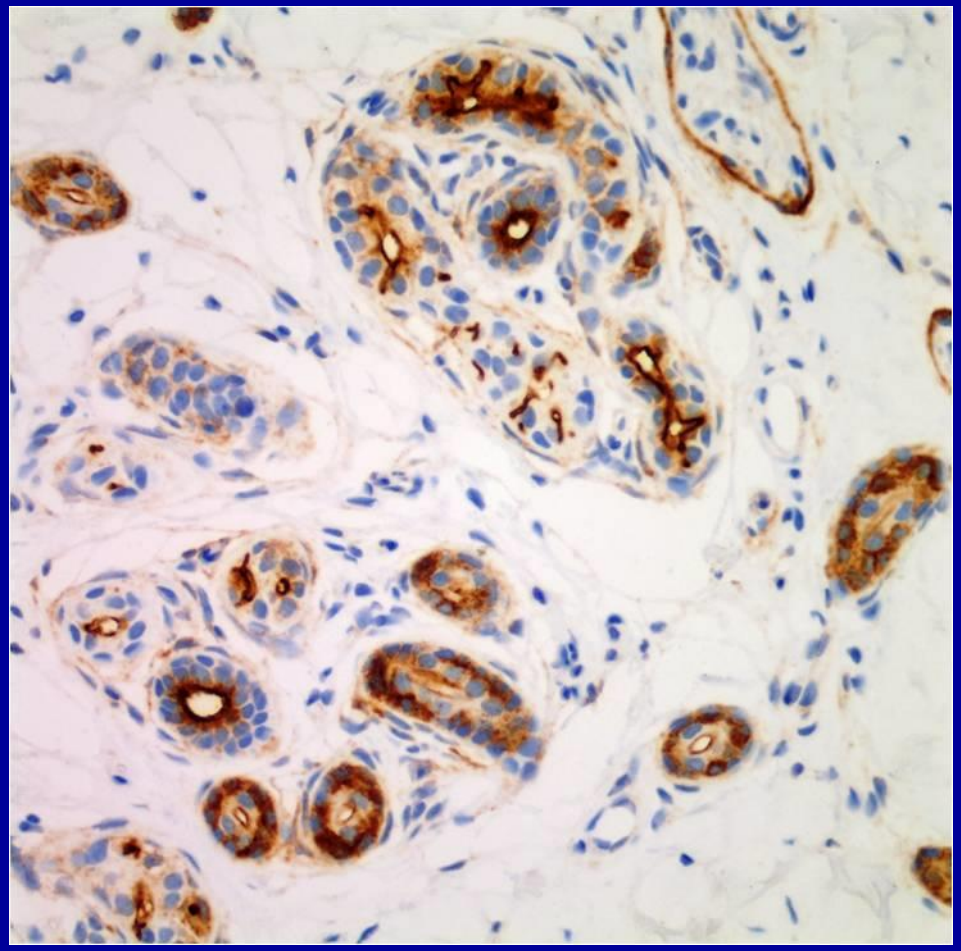


patient

control



Skin Tissue



MUC1 Knockout Mouse

- No clinical disease
- Many mucoproteins
  - Some functions may be interchangeable

MUC1

- Mutant seen in many tissues
- Only causes kidney disease

- In the knockout mouse, MUC1 does not have an essential function.

- All patients have a mutation producing the same mutant peptide.

Hypothesis

- There are many mucoproteins, and their function overlaps.
- The absence of MUC1 is not important.
- There is some property of renal tubular cells that make them very sensitive to the abnormal MUC1, leading to slowly progressive cell death.

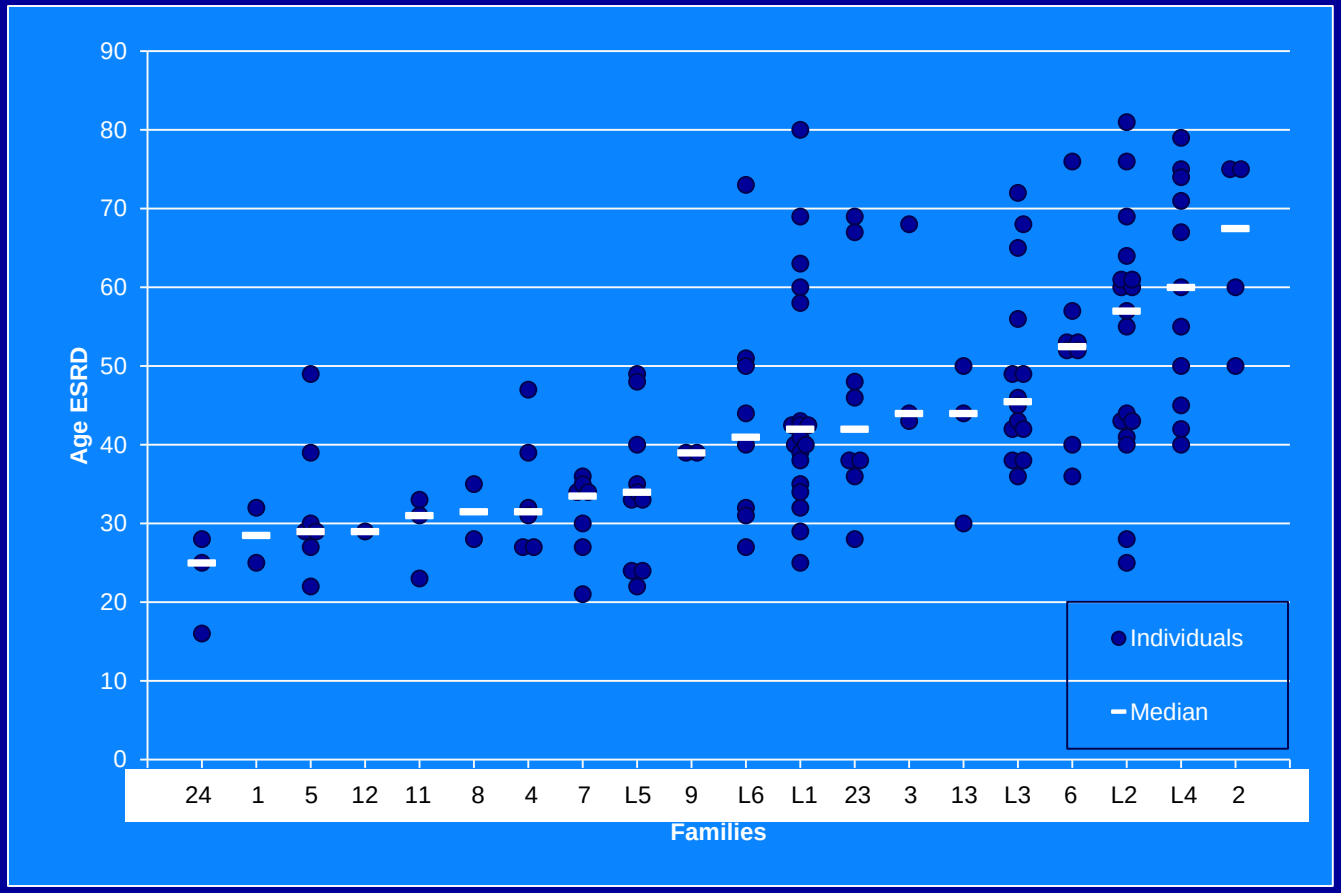
Clinical Characterization

- 35 imaging studies (70 kidneys)
  - Normal or small kidneys
  - 49/70 kidneys no cysts
  - 13/70 had one cyst
  - No medullary cysts
  - MCKD not suspected on any ultrasound
  - CKD was most common diagnosis

Clinical Characterization

- 34 renal biopsies reviewed:
  - All showed tubulo-interstitial kidney disease
  - 4 microcystic dilation of the tubules
    - 2 suggested medullary cystic kidney disease
    - 1 suggested polycystic kidney disease
    - 1 suggested tubular toxic injury

ESRD According to Family

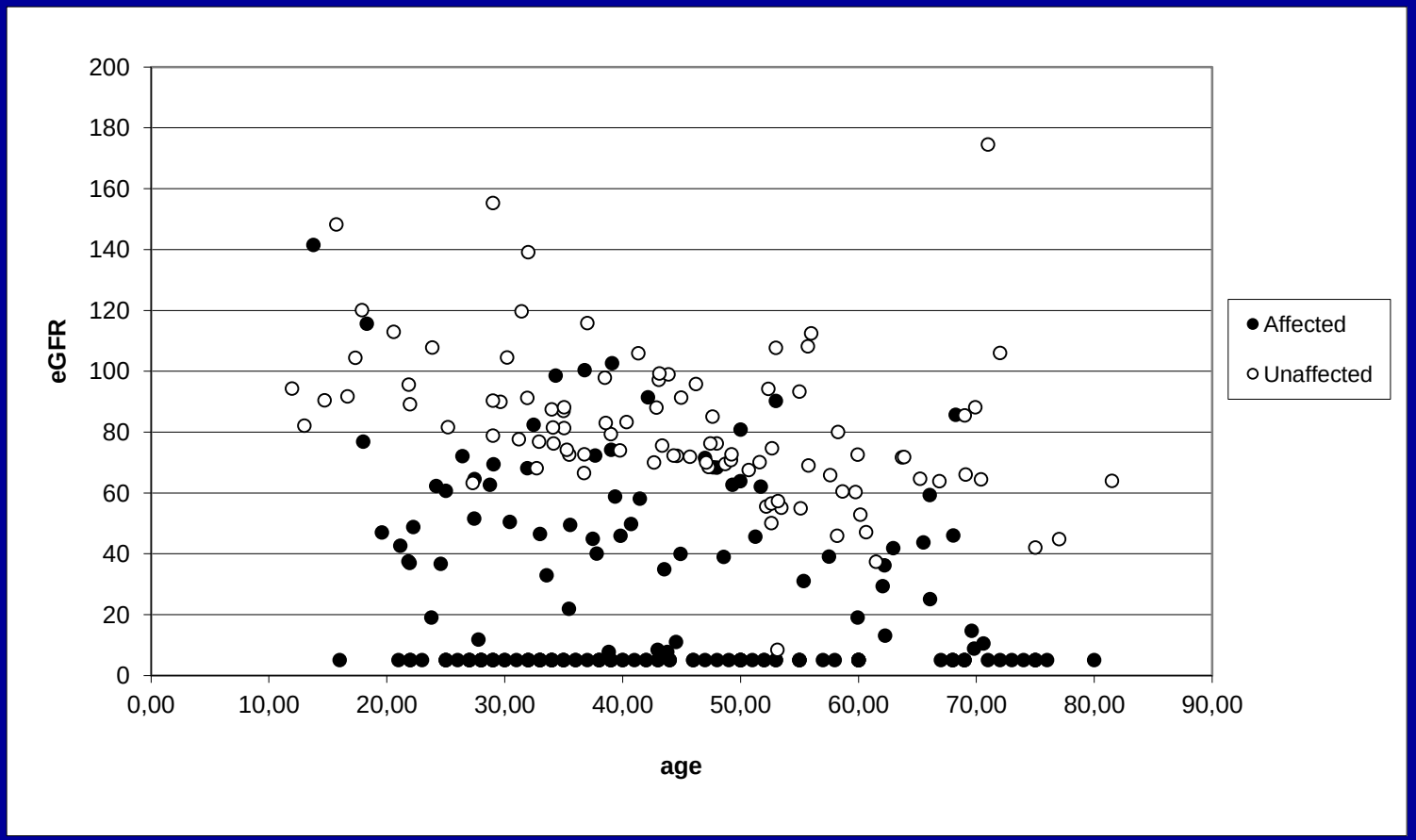


Development of Genotyping Assay

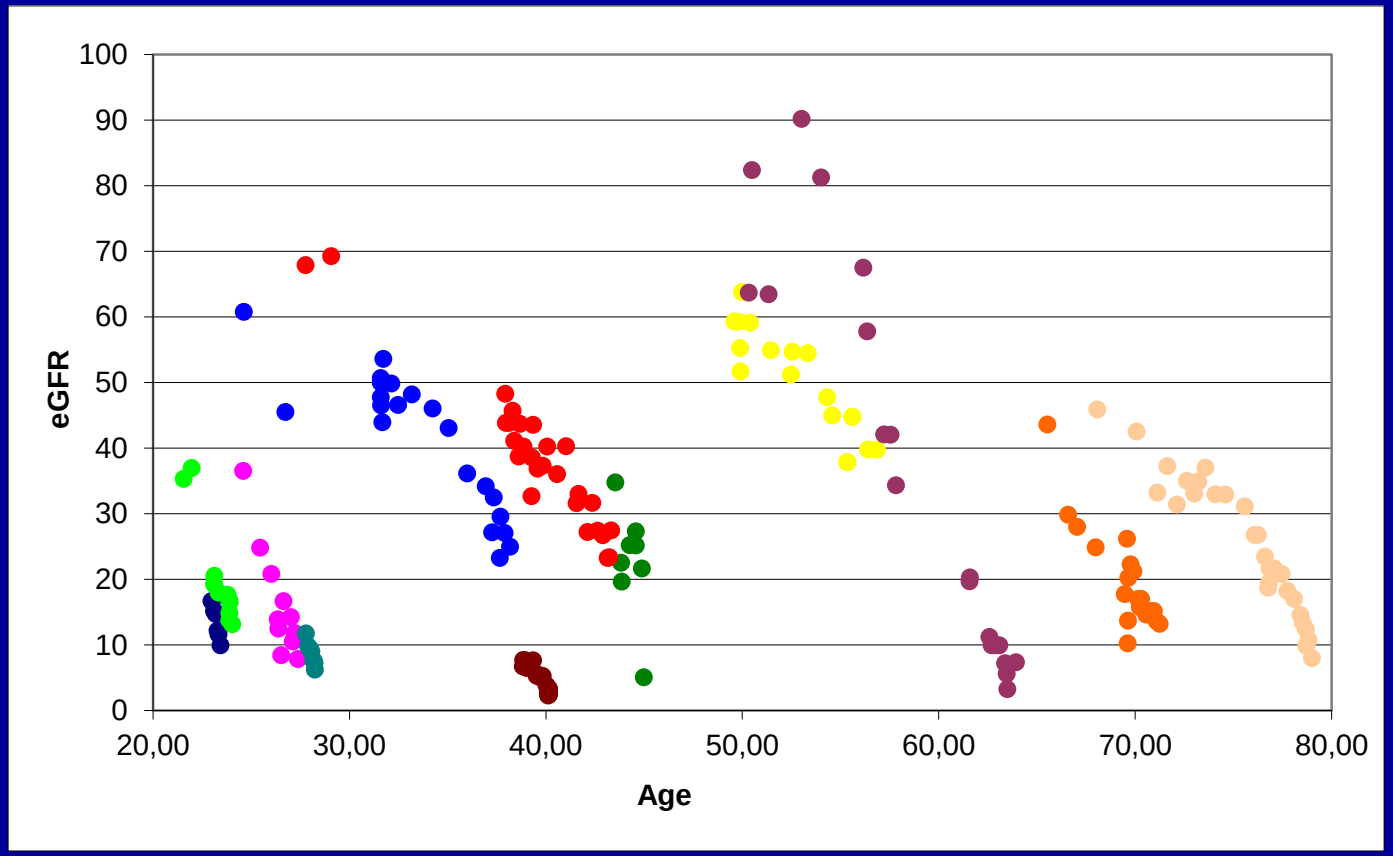
- 21 additional potential families identified
  - 18 families had the insertion
- All 24 families to date have the same type of mutation
- We have subsequently identified another 20 families with the same type of mutation

Mutation	UMOD	REN	MUC 1
Loss of normal gene function	↑Urate Gout	↓BP, Hgb ↑K, Urate	No other symptoms
Tx of loss of fxn	Allopurinol	Fludrocortisone	Supportive
Knockout mouse	No effect	Death in utero	No effect
Gene deletion or truncation	No effect	No effect	No effect
Abnormal production	Intracellular deposition, Kidney failure	Intracellular deposition, Kidney failure	Intracelular deposition, Kidney failure

eGFR of MCKD1 Affected and Unaffected Individuals



eGFR Decline in 12 MCKD1Individuals



eGFR change ≥ 50 ml/min .99 ± 6 ml/in/year
eGFR change < 50 ml/min -6.7 ± 4 ml/in/year
p<0.001

Treatment

- Supportive
- Follow eGFR closely when <50 ml/min

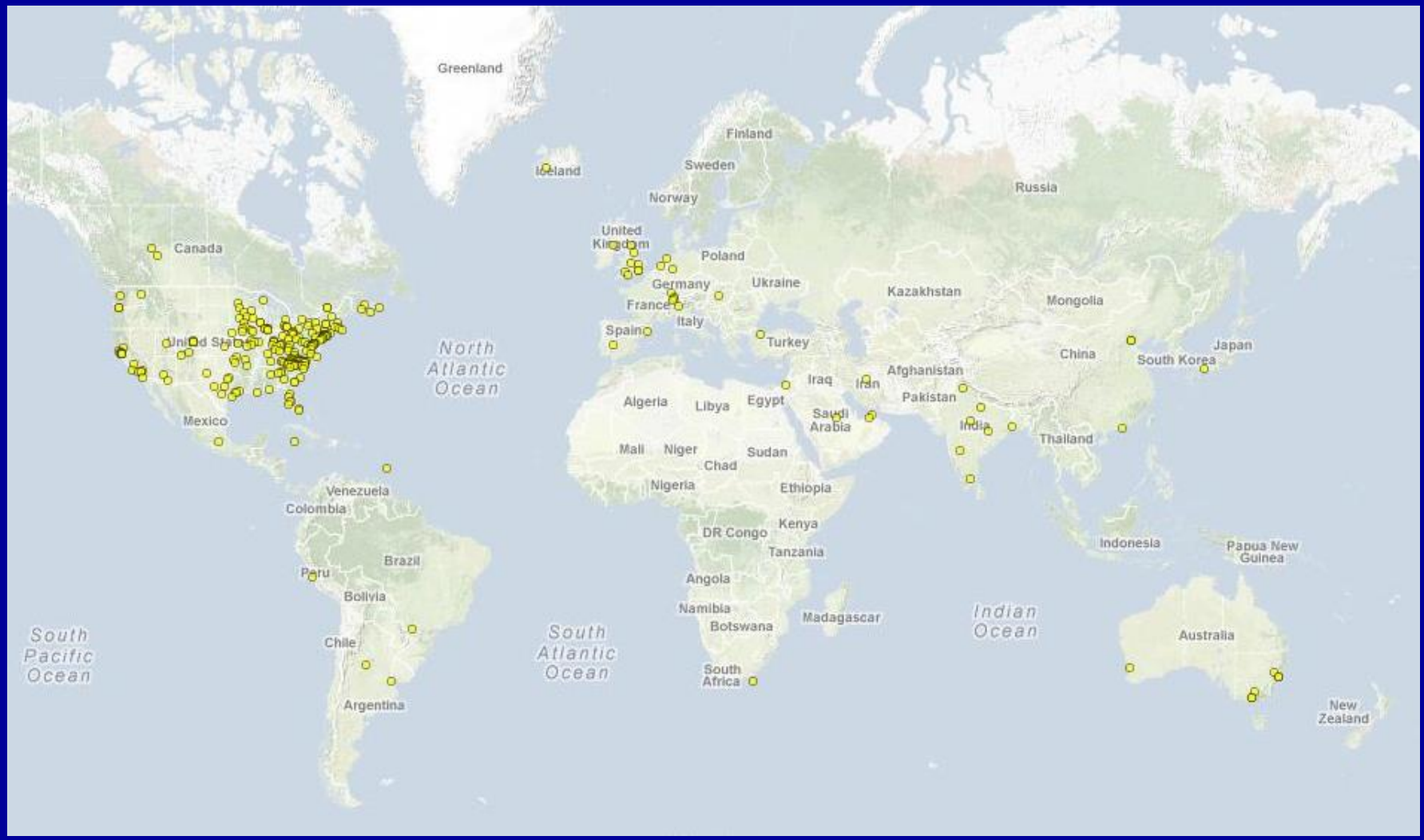
- Do not allow kidney donation without genetic testing for the mutation

Issues to Reconcile

- How does mutant MUC1 contribute to pathology
- Why is pathology found only in the kidney?
- Why is there a variable rate of expression?

Identifying Families

- 450 families to date have contacted us
- 90 are positive for *UMOD* mutation
- 6 are positive for *REN* mutation
- 24 families with *MUC1* mutation


Greenland
Iceland
Finland
Sweden
Norway
Russia
United Kingdom
Poland
Germany
Ukraine
Kazakhstan
Mongolia
France
Italy
Spain
Turkey
China
Japan
South Korea
Canada
United States
North Atlantic Ocean
Afghanistan
Iraq
Iran
Pakistan
Algeria
Libya
Egypt
Saudi Arabia
India
Thailand
Mexico
Mali
Niger
Sudan
Chad
Nigeria
Ethiopia
Venezuela
Colombia
Kenya
DR Congo
Tanzania
Indonesia
Papua New Guinea
Brazil
Peru
Angola
Bolivia
Namibia
Botswana
Madagascar
Indian Ocean
South Pacific Ocean
South Atlantic Ocean
Australia
Chile
South Africa
Argentina
New Zealand

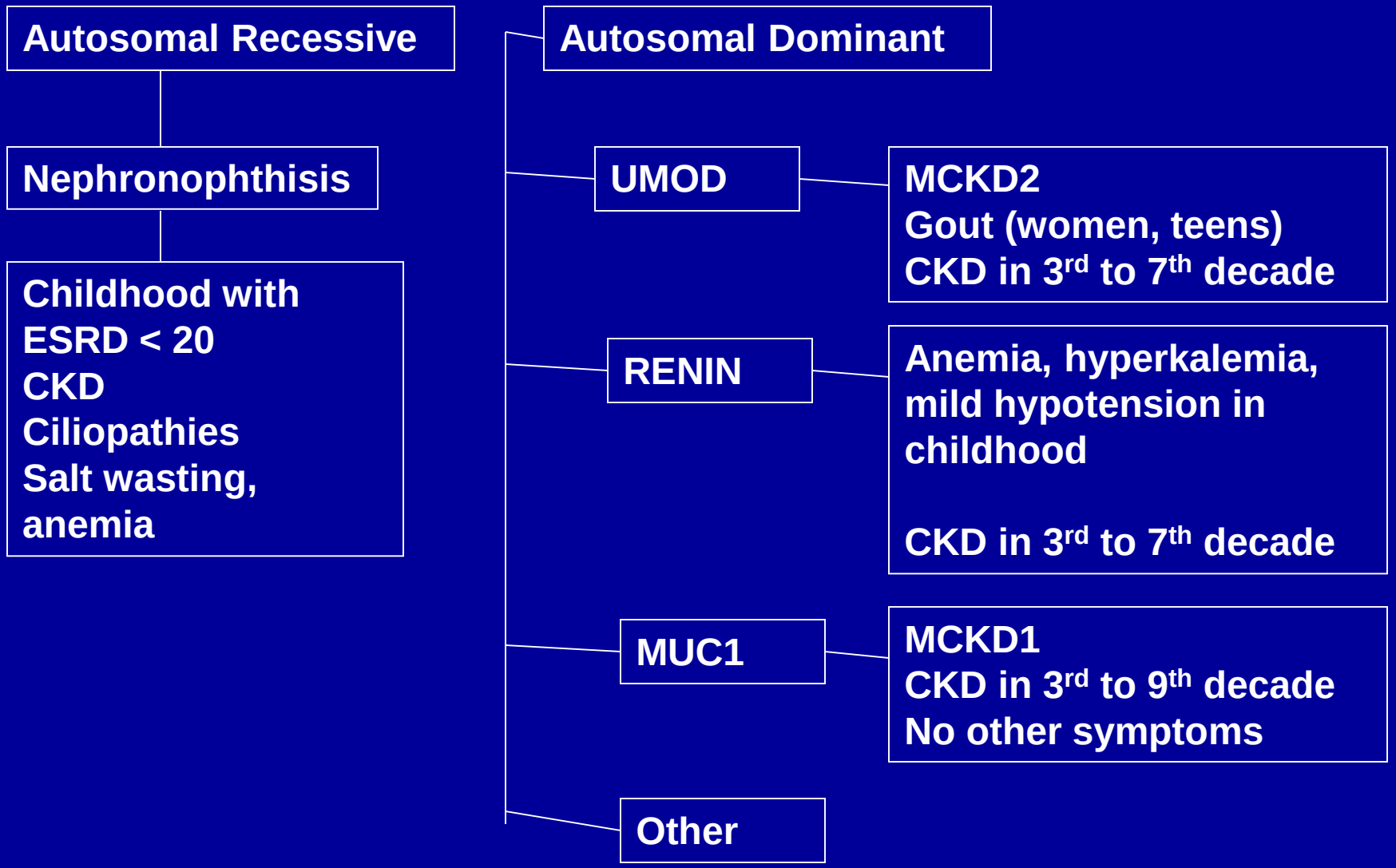
Challenges

- Uncommon disorders
- Confusing terminology
- Predominant interest in glomerular disease
- Kidney biopsies are not diagnostic

Genetic Testing

- Available in a research setting
- Remains extremely difficult to do
- Contact me (ableyer@wakehealth.edu) for information

Inherited Tubulo-Interstitial Kidney Disease



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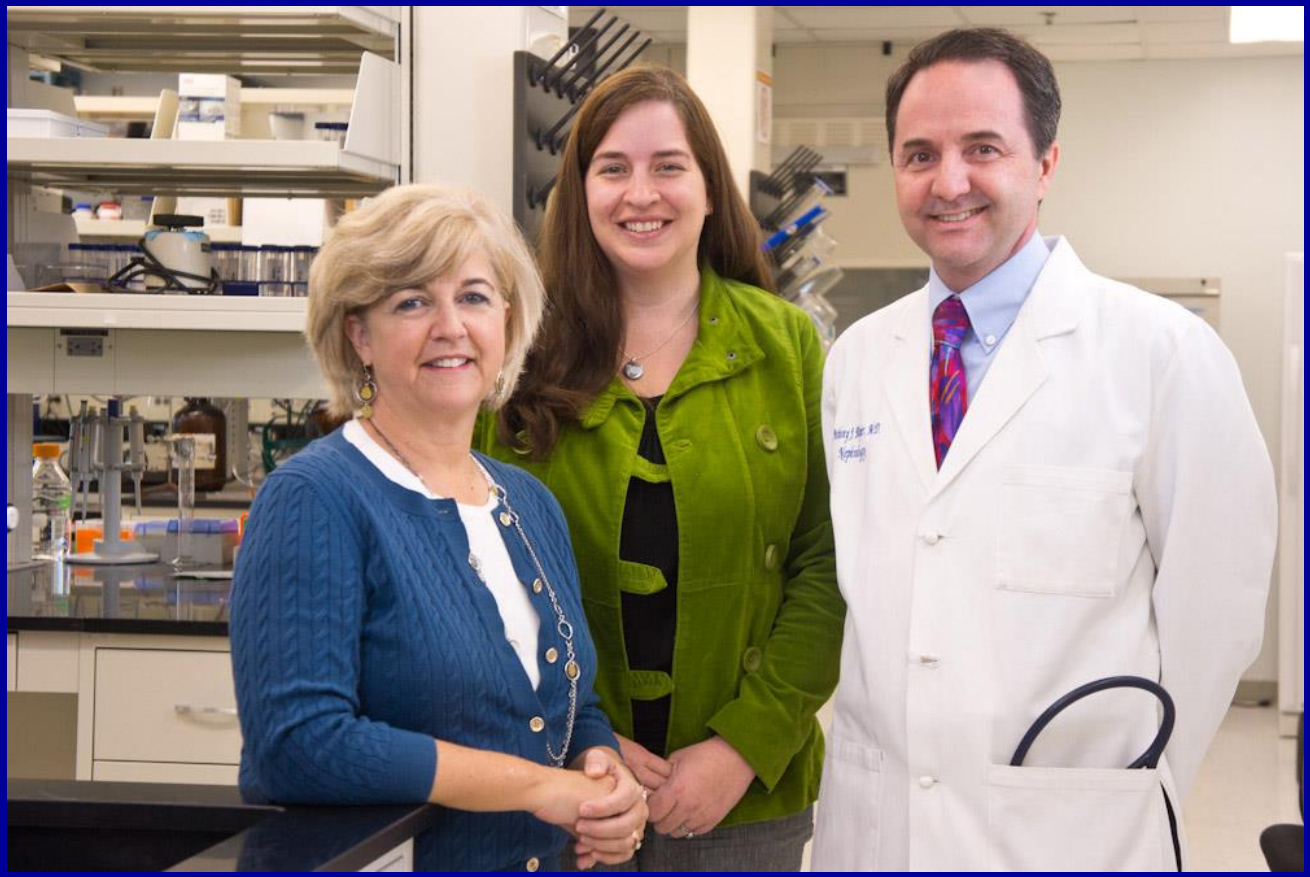
Research Team

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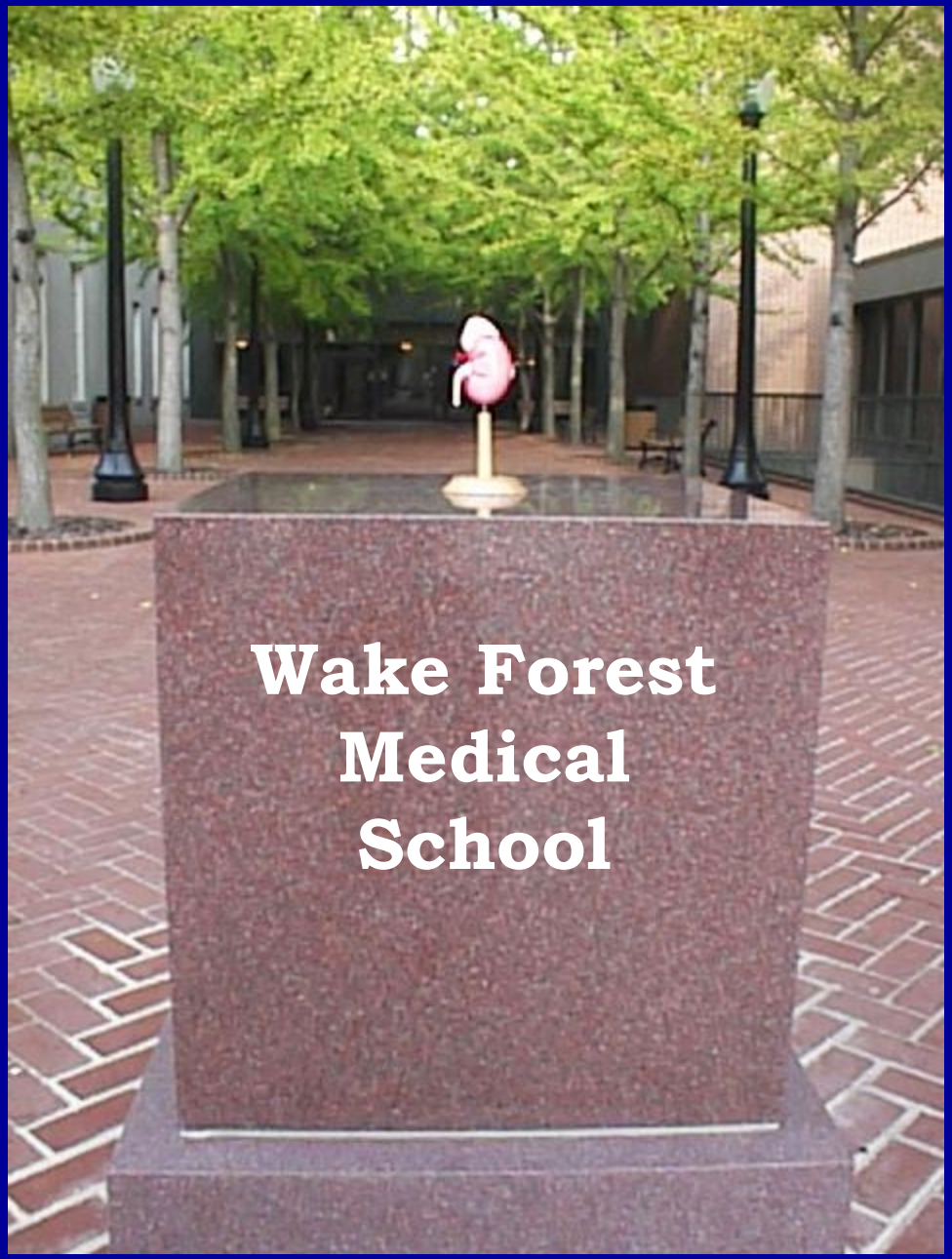
Stanislav
group leader
Petr
protein analysis
Mirek
DNA sequencing
Katerina
cell biology
MCKD group Prague
04/17/2012


Wake Forest
Medical
School

Uromodulin

MOVE

- A ZP domain protein

- Carboxy terminal membrane domain
- Filaments are cross linked
- Heavily glycosylated

Uromodulin

MOVE

- 75,000 kD protein
- Monomers come together to form polymer that is heavily glycated
- VERY insoluble

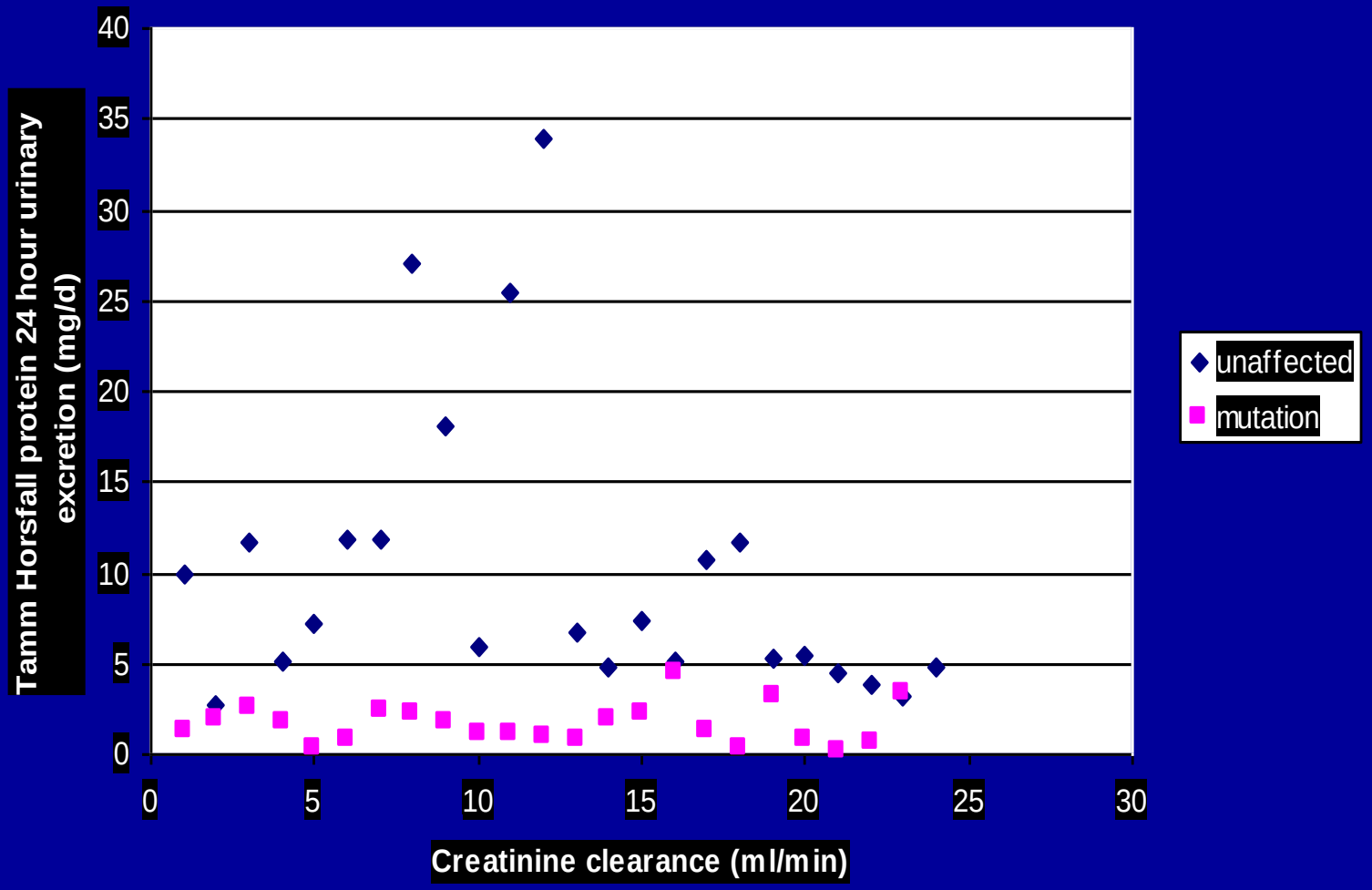
THP Production

MOVE

- Conversion of precursor (84 kD) to mature form (97kD) depends on processing of glycans in the Golgi apparatus

Serafini-Cessi F, et al. Biochem Biophys Res Comm 1993

Figure 2. Tamm Horsfall Protein Excretion According to Creatinine Clearance



Clinical Presentation

Nephronophthisis	ADTKD (UMOD and MUC1)
Rare	Rare
Autosomal recessive	Autosomal dominant
Salt-wasting, fatigue	
Anemia	
	Gout in teen years (UMOD)
Median ESRD 13 years	Median ESRD 40
Bland urinary sediment	Bland urinary sediment
Bx: tubulo-interstitial scarring	Bx: tubulo-interstitial scarring

Conditions would not be difficult to distinguish, except for confusing terminology, early misunderstanding, and their rarity.


Washington
Oregon
Montana
North Dakota
Minnesota
Maine
Vermont
New Hampshire
Idaho
South Dakota
Wisconsin
Michigan
New York
Massachusetts
Rhode Island
Connecticut
Wyoming
Nebraska
Iowa
Pennsylvania
New Jersey
Delaware
Maryland
Nevada
California
Utah
Colorado
Kansas
Illinois
Ohio
Indiana
West Virginia
Virginia
Kentucky
Missouri
Tennessee
North Carolina
Arizona
New Mexico
Oklahoma
Arkansas
South Carolina
Georgia
Mississippi
Alabama
Texas
Louisiana
Florida
Hawaii
Alaska