Autosomal Dominant Tubulo-Interstitial Kidney Disease

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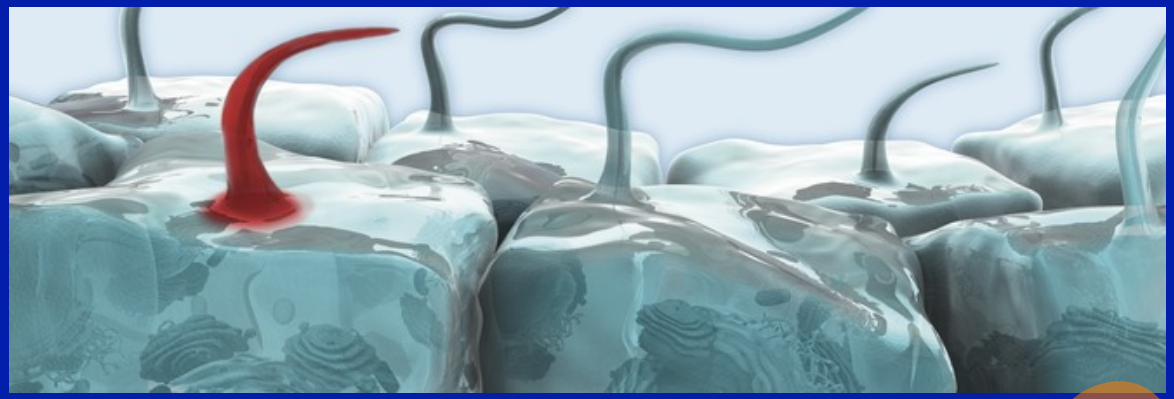
1944	Thorn and Kopf describe a young man with salt wasting and CKD
1951	Fanconi describes two families with autosomal recessive kidney disease in childhood. “Nephronophthisis
1960	Duncan and Dixon describe inherited gout and kidney disease
1962	Straus : 18 cases of cystic disease of the renal medulla: only 2 inherited
1966	Goldman and Gardner identify five generation family with inherited kidney disease
1966-1980	For some reason clinicians cannot determine that there are recessive and dominant forms of the disease.

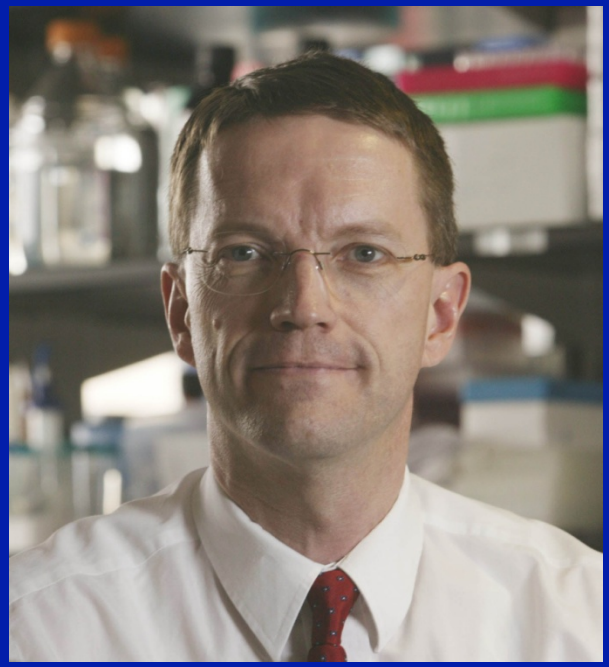
1990's	Cameron and Stewart describe a number of families with juvenile hyperuricemia and kidney disease. Allopurinol prevents progression
1999	Dahan et al propose that MCKD2 and FJHN are the same disease
2001	*UMOD* mutations identified
2011	*REN* mutations identified
2013	*MUC1* mutations identified

- Genetics has sorted out the diseases but terminology remains a problem!

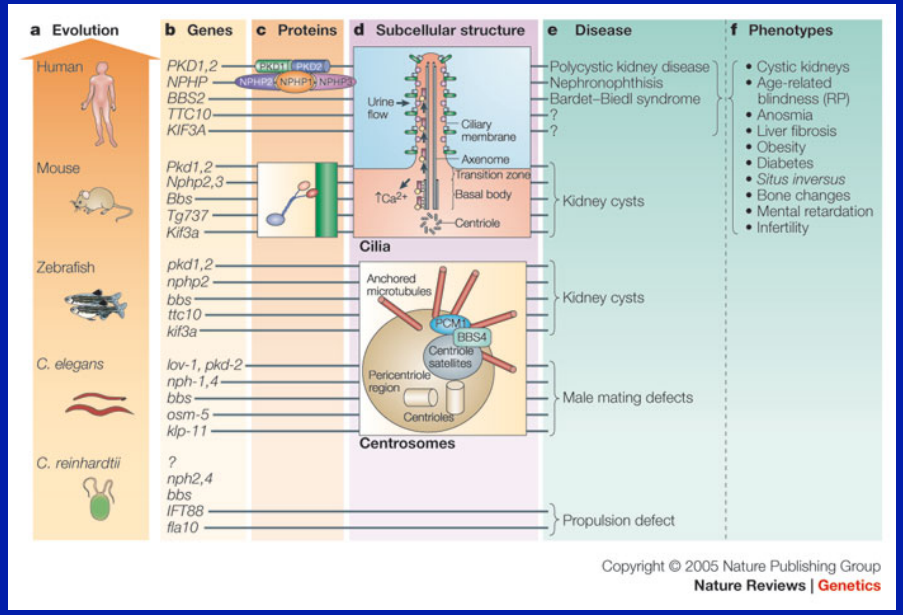


Corinne Antignac, MD

KDIGO



Friedhelm Hildebrandt, MD



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

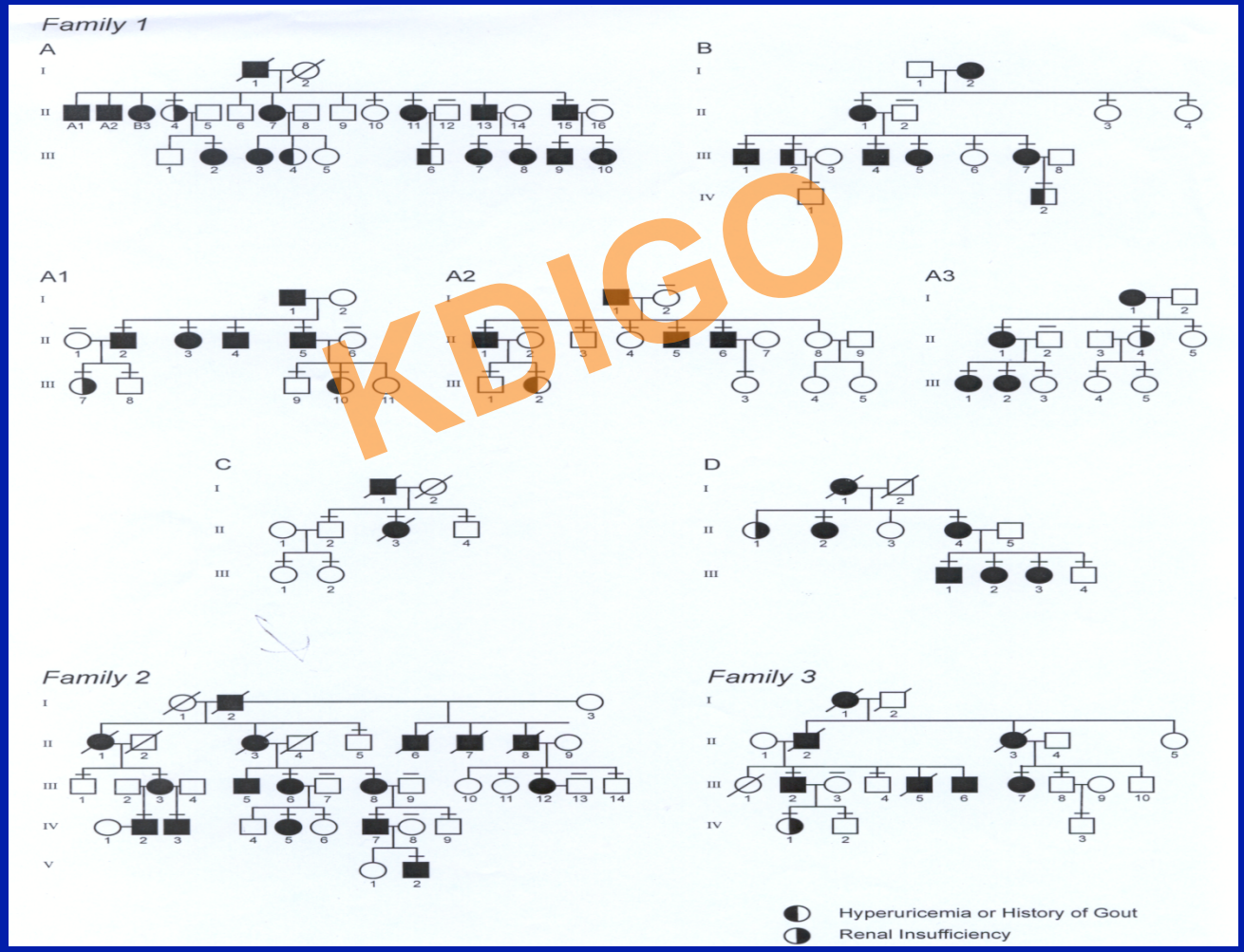
MCKD1
CKD in 3rd to 9th decade
No other symptoms

Other

First Case 4/18/96

- 41 year old white male
  - Gout in late teens
  - Father, brother, 2 uncles and one aunt with gout and kidney disease
  - Serum Creatinine 3.2 mg/dl
  - Serum uric acid 7.2 mg/dl on allopurinol
  - Bland urinalysis

Family Tree


Family 1
A
B
A1
A2
A3
C
D
Family 2
Family 3
KDIGO
Hyperuricemia or History of Gout
Renal Insufficiency

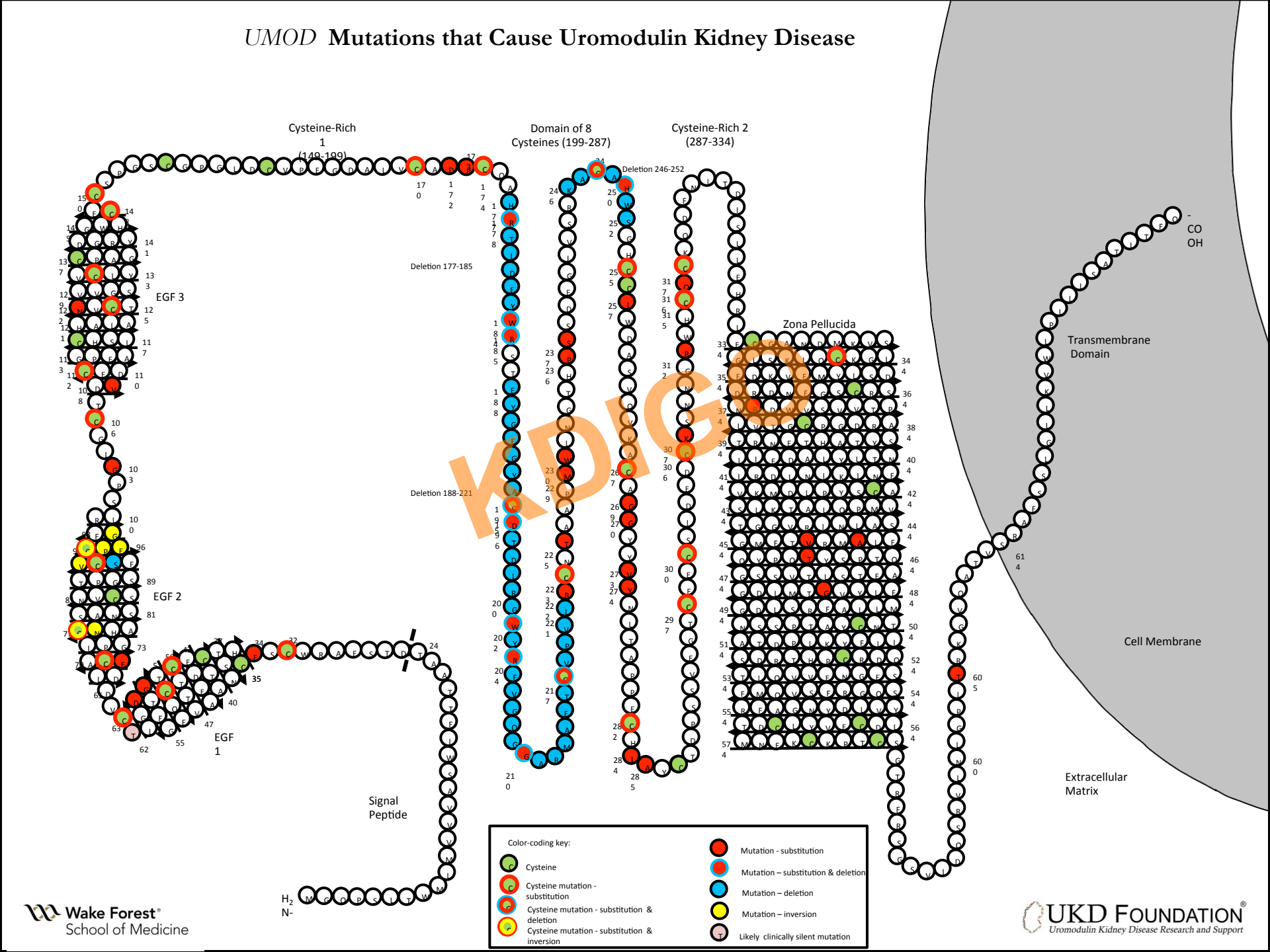
MCKD2

- Mutations in uromodulin identified as cause of disease
- Gout is found in almost all the families with this disorder
- All families are hyperuricemic

Uromodulin Mutations

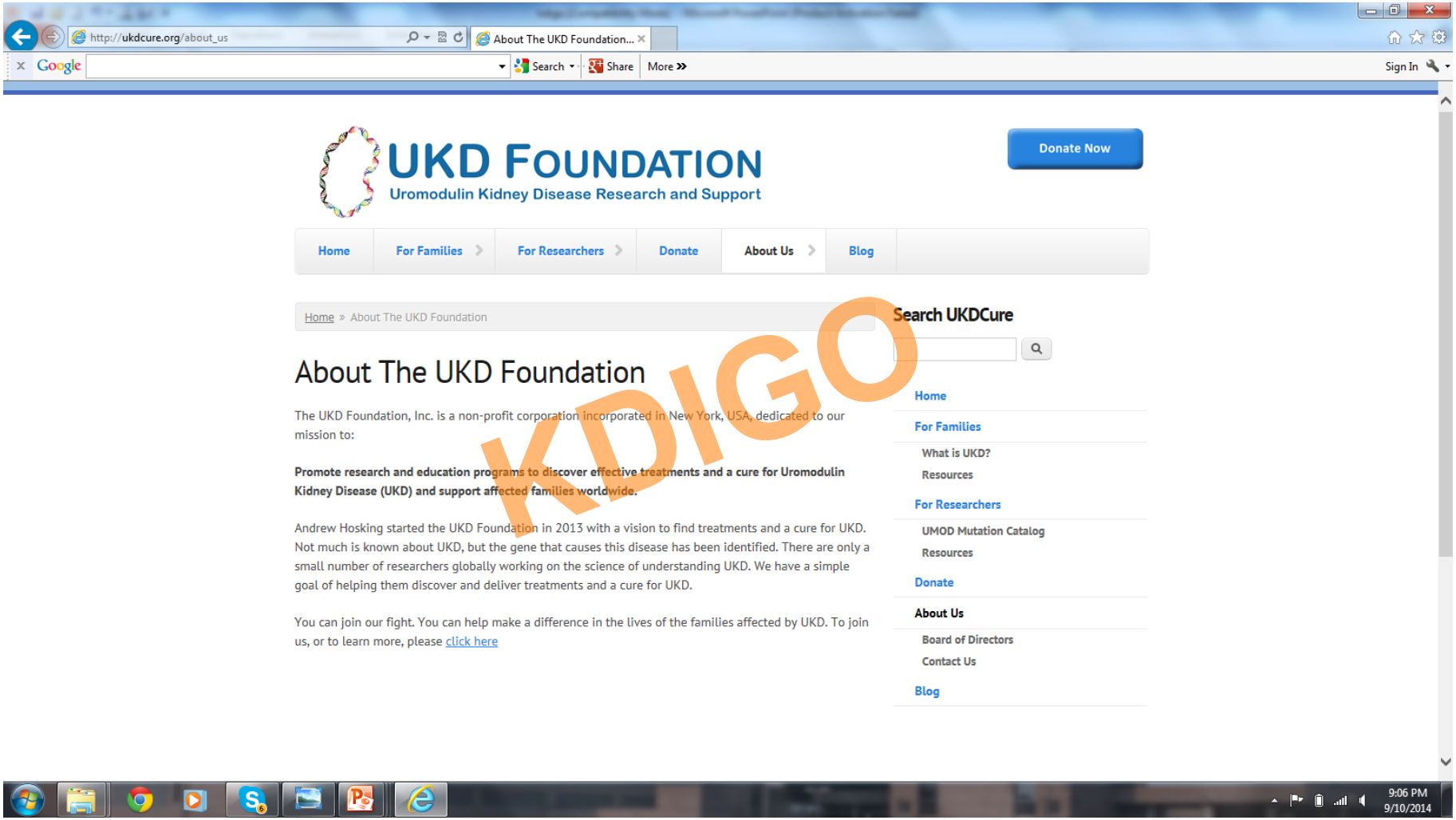
- Result in deposition of mutant uromodulin in the ER
- Most mutations involve a cysteine

UMOD Mutations that Cause Uromodulin Kidney Disease



Wake Forest School of Medicine

UKD Foundation
Uromodulin Kidney Disease Research and Support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Uromodulin Kidney Disease Research and Support
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About The UKD Foundation
The UKD Foundation, Inc. is a non-profit corporation incorporated in New York, USA, dedicated to our mission to:
Promote research and education programs to discover effective treatments and a cure for Uromodulin Kidney Disease (UKD) and support affected families worldwide.
Andrew Hosking started the UKD Foundation in 2013 with a vision to find treatments and a cure for UKD. Not much is known about UKD, but the gene that causes this disease has been identified. There are only a small number of researchers globally working on the science of understanding UKD. We have a simple goal of helping them discover and deliver treatments and a cure for UKD.
You can join our fight. You can help make a difference in the lives of the families affected by UKD. To join us, or to learn more, please click here
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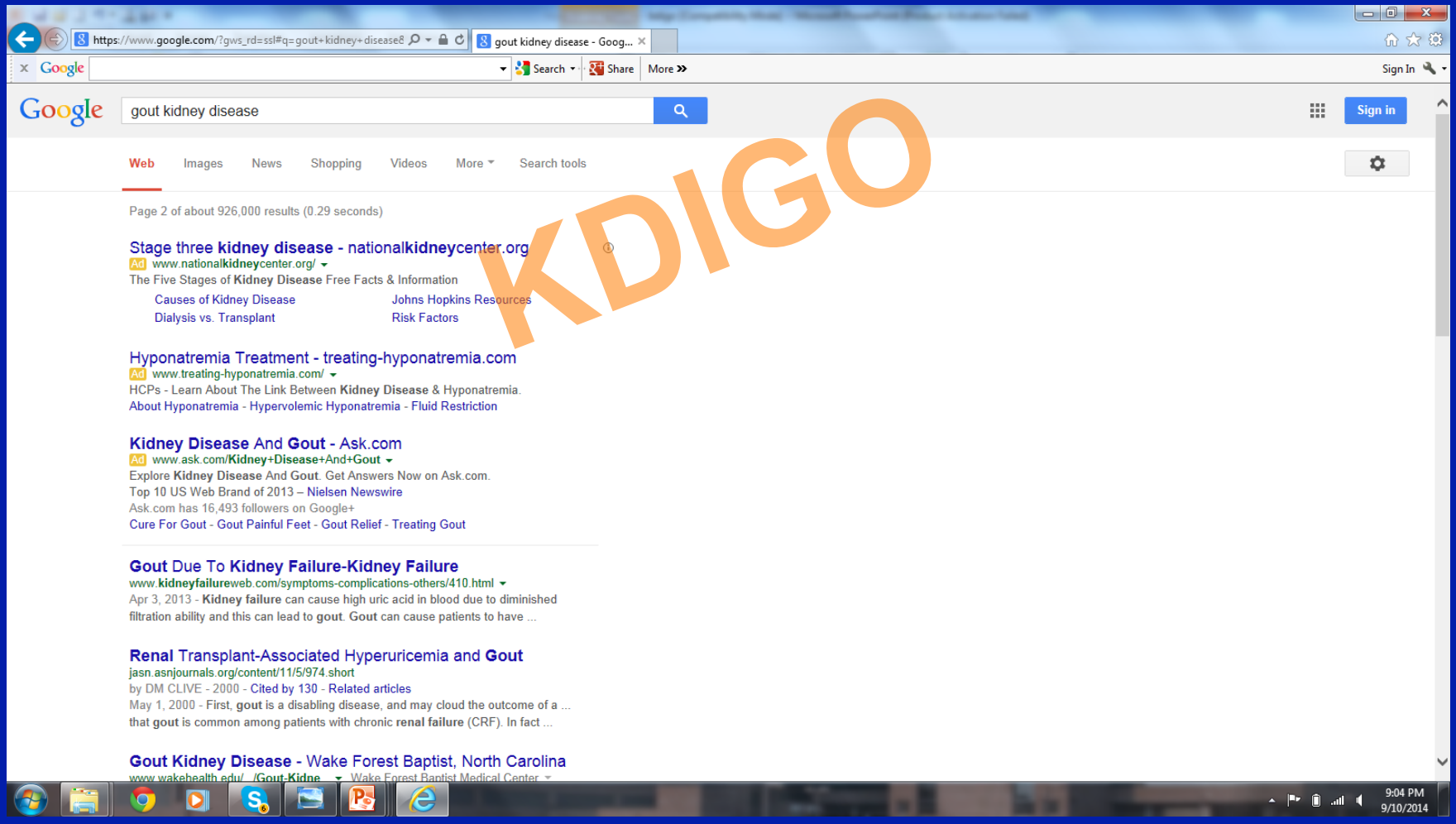
Diagnosis

- Fairly straightforward
- Gout is such an important sign of the disease and recognized easily by family members
- Most clinicians recognize the gout as a factor
- UMOD mutational analysis available clinically

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

What's in a name?



Case #2

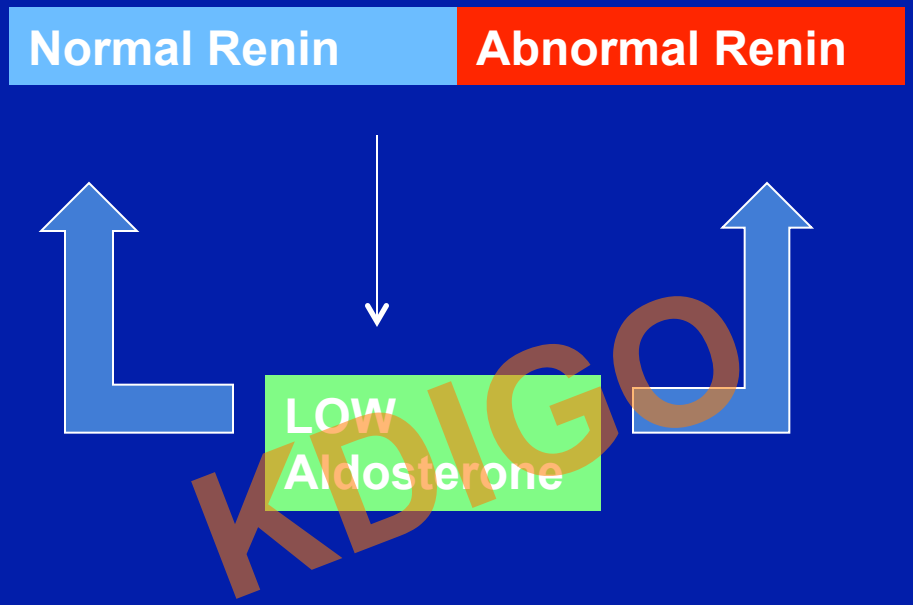
- 8 year old girl
  - Developed acute kidney injury after a bout of fever treated with NSAID's
  - Anemia
  - Hyperuricemia
  - Mild hypotension
  - Chronic kidney disease
- Father also had slowly progressive chronic kidney disease and anemia as a child

Dominant Renin Gene Mutations Associated with Early-Onset Hyperuricemia, Anemia, and Chronic Kidney Failure

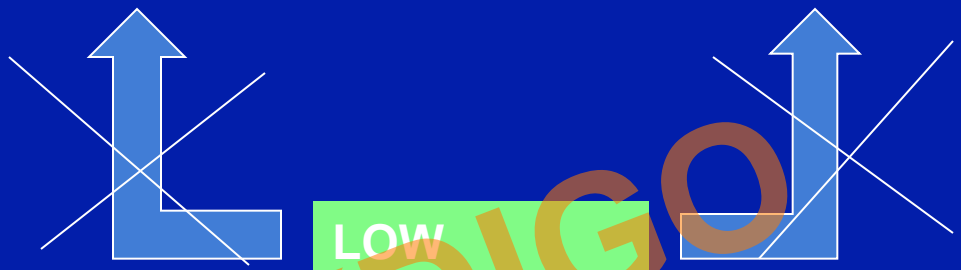
Martina Živná,[1,2] Helena Hůlková,[2] Marie Matignon,[4,5] Kateřina Hodaňová,[1,2] Petr Vyleťal,[1,2] Marie Kalbáčová,[1,2] Veronika Barešová,[1,2] Jakub Sikora,[2] Hana Blažková,[2] Jan Živný,[3] Robert Ivánek,[1,2] Viktor Stránecký,[1,2] Jana Sovová,[2] Kathleen Claes,[6] Evelyne Lerut,[6] Jean-Pierre Fryns,[7] P. Suzanne Hart,[8] Thomas C. Hart,[9] Jeremy N. Adams,[8] Audrey Pawtowski,[10] Maud Clemessy,[12] Jean-Marie Gasc,[12] Marie-Claire Gübler,[11,13] Corinne Antignac,[10,11,13] Milan Elleder,[1,2] Katja Kapp,[14] Philippe Grimbert,[4,5] Anthony J. Bleyer,[15] and Stanislav Kmoch[1,2,*]

Characteristics

- Low renin
  - Anemia from birth until puberty
  - Mildly elevated potassium
  - Mildly low blood pressure
  - **Prone to acute kidney injury
- mREN
  - Intracellular deposition
  - Progressive kidney disease



Normal Renin | Abnormal Renin



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	1.3	1825
-1wk		87.6	5.6	1.6	2275
1wk	106/69	90	4.2	1.1	2450
6wks	112/67		4.3	1.0	2675

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	
Abnormal production	Intracellular deposition, Kidney failure	Intracellular deposition, Kidney failure	

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

Andi Gnirke
Dave Jaffe
Chad Nusbaum

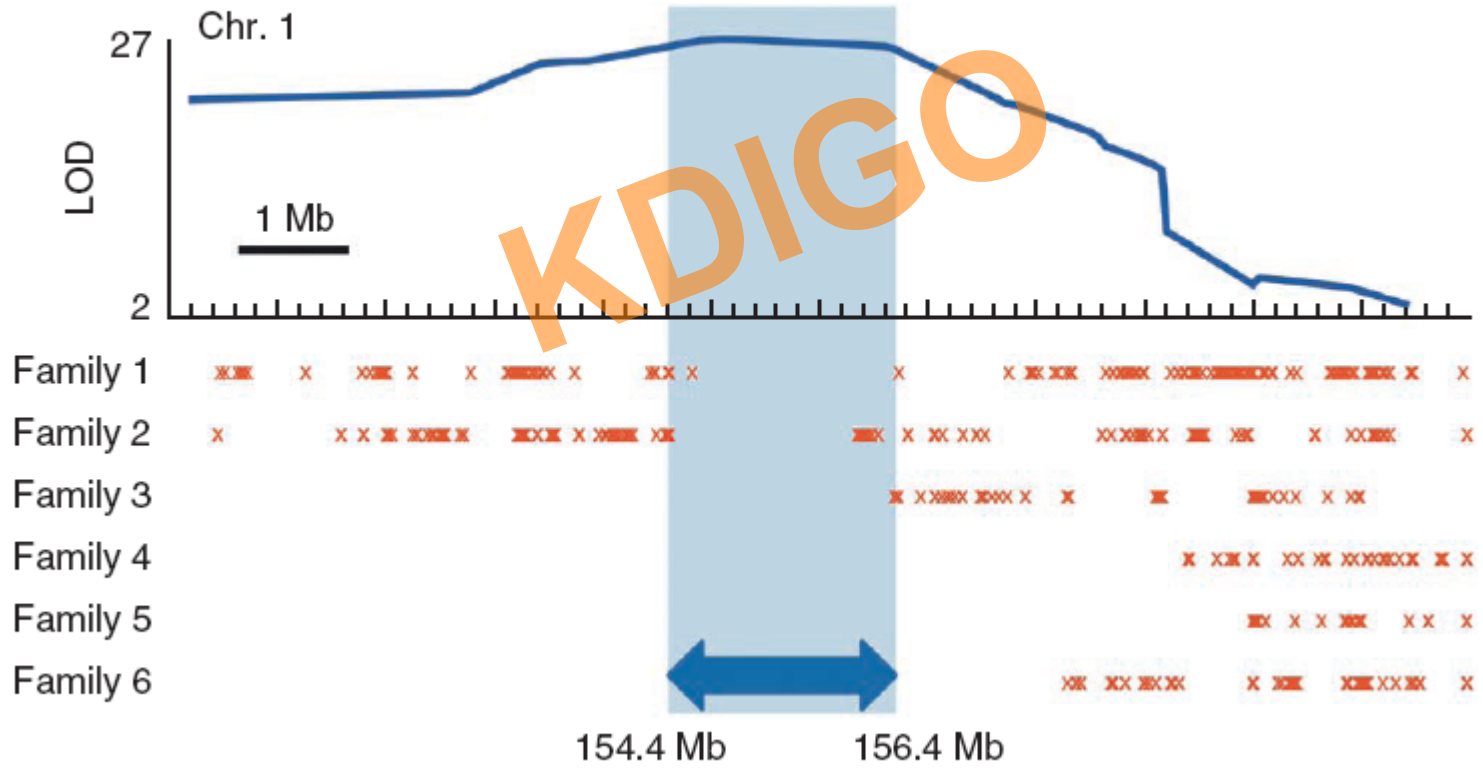
DNA sequencing

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

Clinical Phenotyping & Functional Insights

Tony Bleyer
Suzanne Hart

Linkage of 6 MCKD1 families to Chromosome 1



Broad Institute

- 2 individuals from 6 linked families underwent whole exome analysis
- RESULTS: No mutations
- 99.9% of the genome excluded ☺

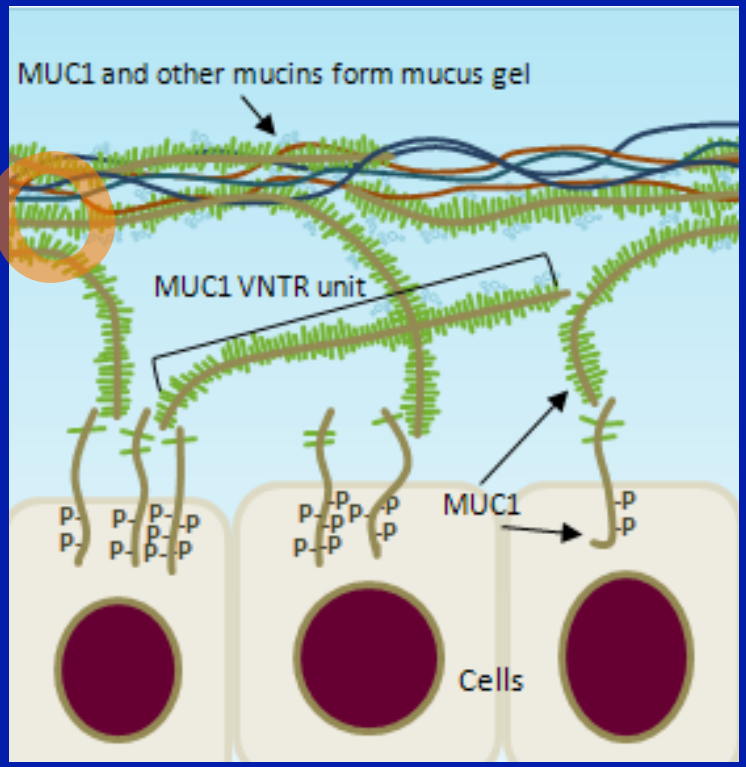
nature genetics

Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in *MUC1* missed by massively parallel sequencing

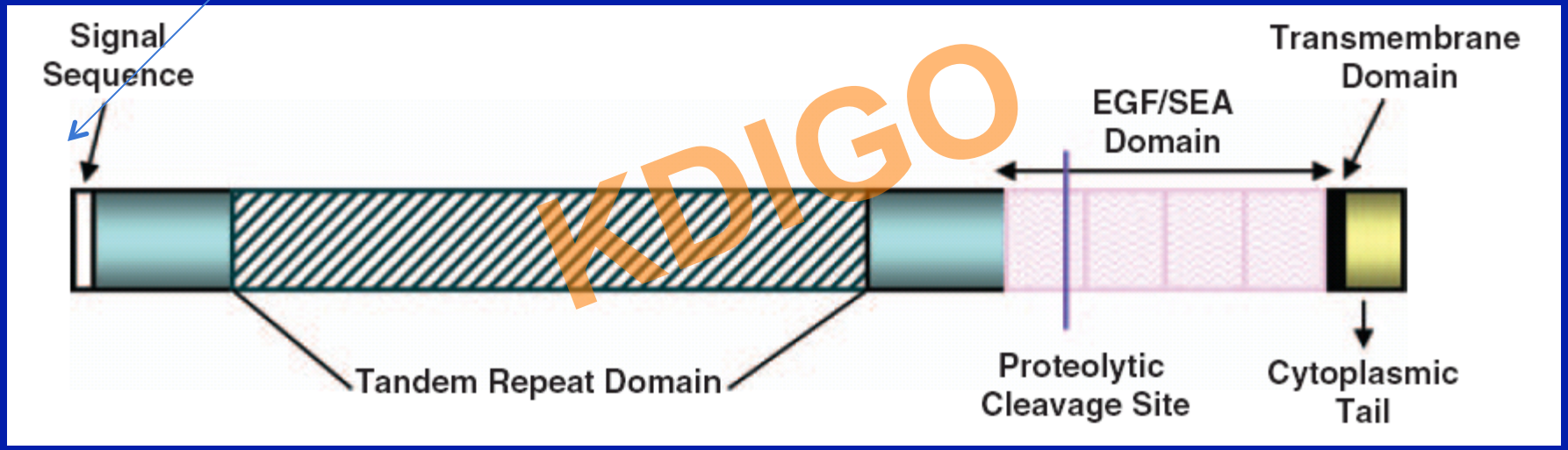
Andrew Kirby[1,2], Andreas Gnirke[1], David B Jaffe[1], Veronika Barešová[3], Nathalie Pochet[1,4], Brendan Blumenstiel[1], Chun Ye[1], Daniel Aird[1], Christine Stevens[1], James T Robinson[1], Moran N Cabili[1,5], Irit Gat-Viks[1,6], Edward Kelliher[1], Riza Daza[1], Matthew DeFelice[1], Helena Hůlková[3], Jana Sovová[3], Petr Vylet'al[3], Corinne Antignac[7–9], Mitchell Guttman[1], Robert E Handsaker[1,10], Danielle Perrin[1], Scott Steelman[1], Snaevar Sigurdsson[1], Steven J Scheinman[11], Carrie Sougnez[1], Kristian Cibulskis[1], Melissa Parkin[1], Todd Green[1], Elizabeth Rossin[1], Michael C Zody[1], Ramnik J Xavier[1,12], Martin R Pollak[13,14], Seth L Alper[13,14], Kerstin Lindblad-Toh[1,15], Stacey Gabriel[1], P Suzanne Hart[16], Aviv Regev[1], Chad Nusbaum[1], Stanislav Kmoch[3], Anthony J Bleyer[17,18], Eric S Lander[1,18] & Mark J Daly[1,2,18]

MUC1

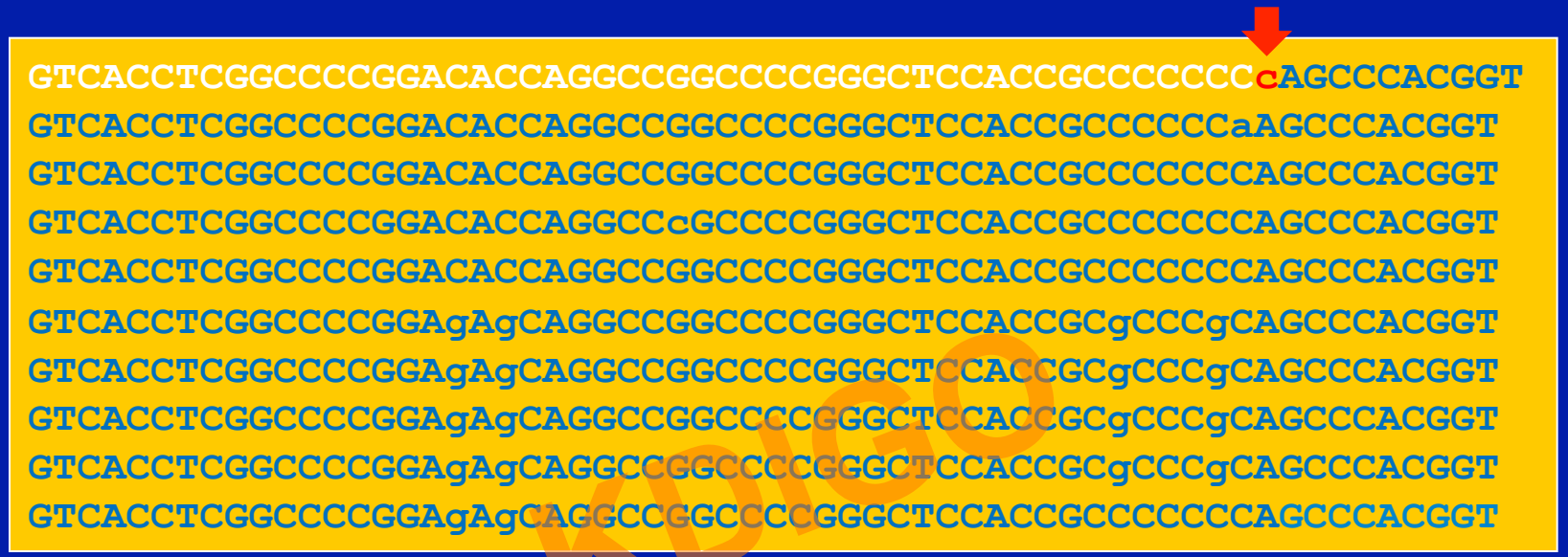
- MUC1 is a membrane-anchored mucoprotein
- Best known in cancer progression
- Expressed in secretory epithelium
- Contains a VNTR unit for glycosylation



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

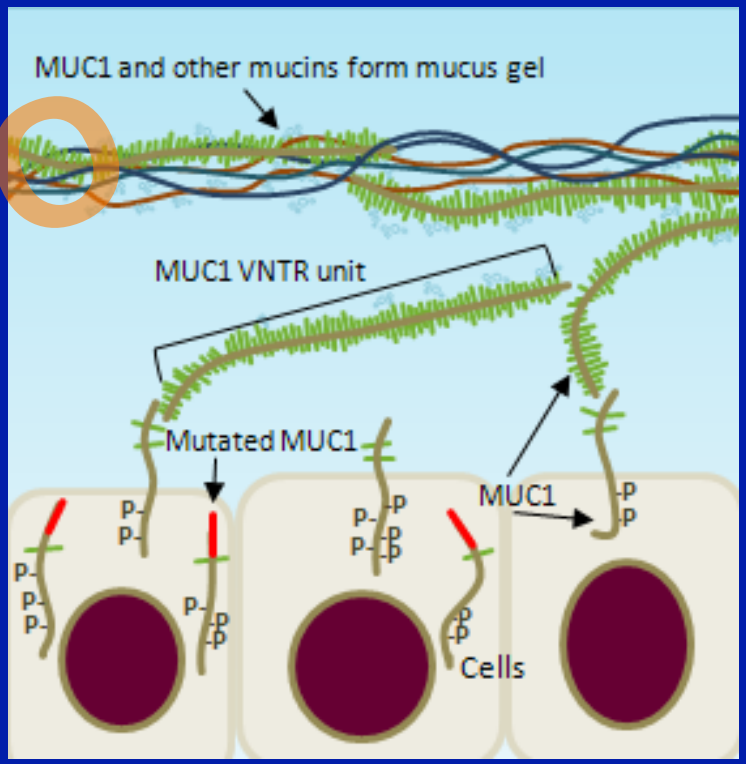
MUC1 Mutation

- 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

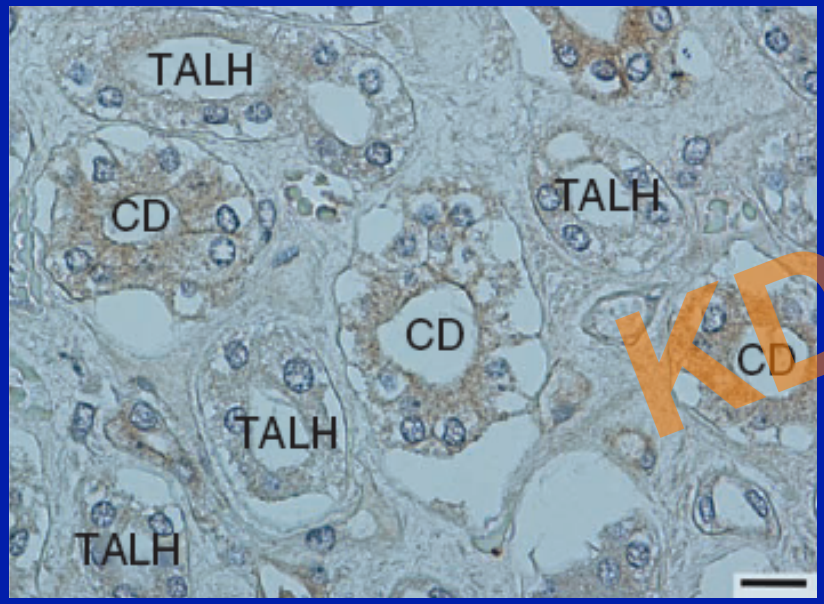
Theoretical Affect of MUC1 insertion

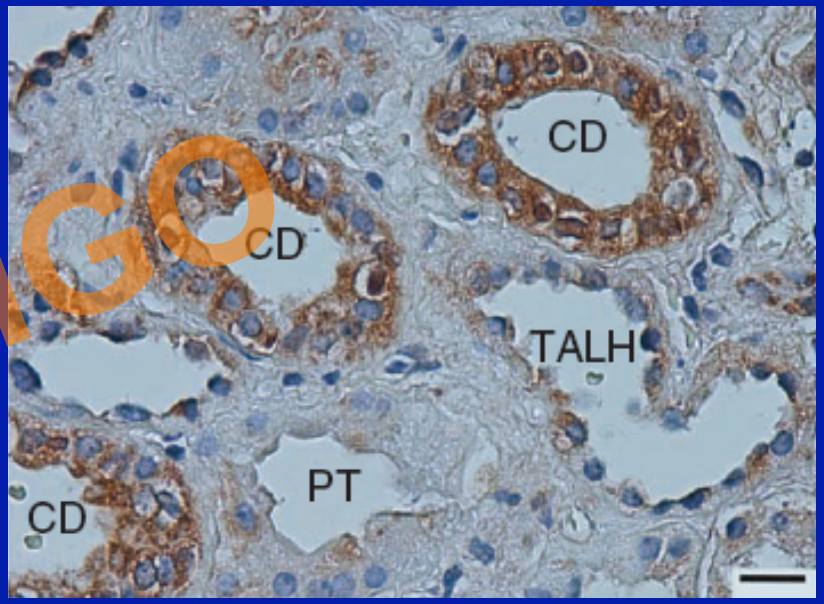
- Mutation is in the VNTR unit
- Causes a frameshift, resulting in VNTR truncation and creation of a neopeptide
- Neopeptide appears to be improperly processed in the cytoplasm
- Leads to apoptosis and slow, progressive tubular cell death



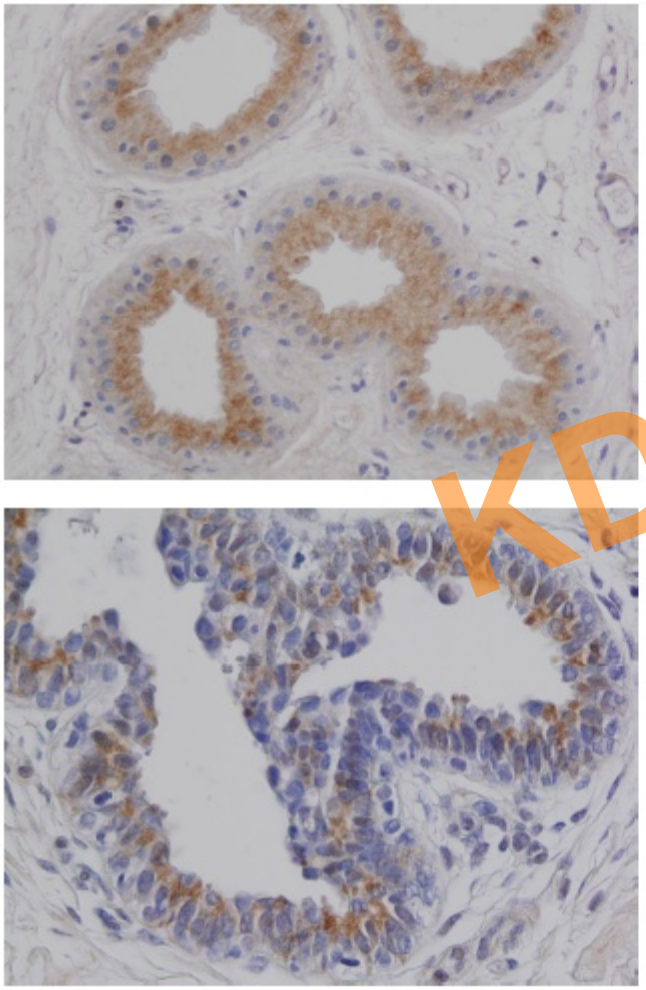
Dr. Stan Kmoch, Charles Medical School,

Normal and Mutant MUC1 Immunostaining by Stan Kmoch, Ph.D.



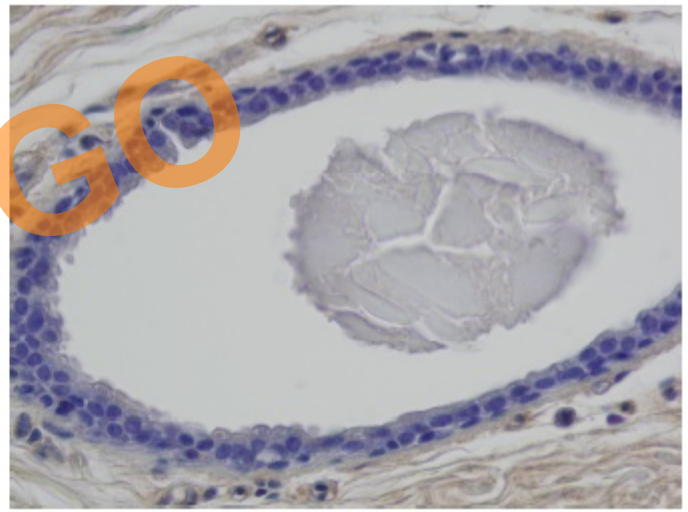


Mutant MUC1 and Breast Tissue by Stan Kmoch



patient

control



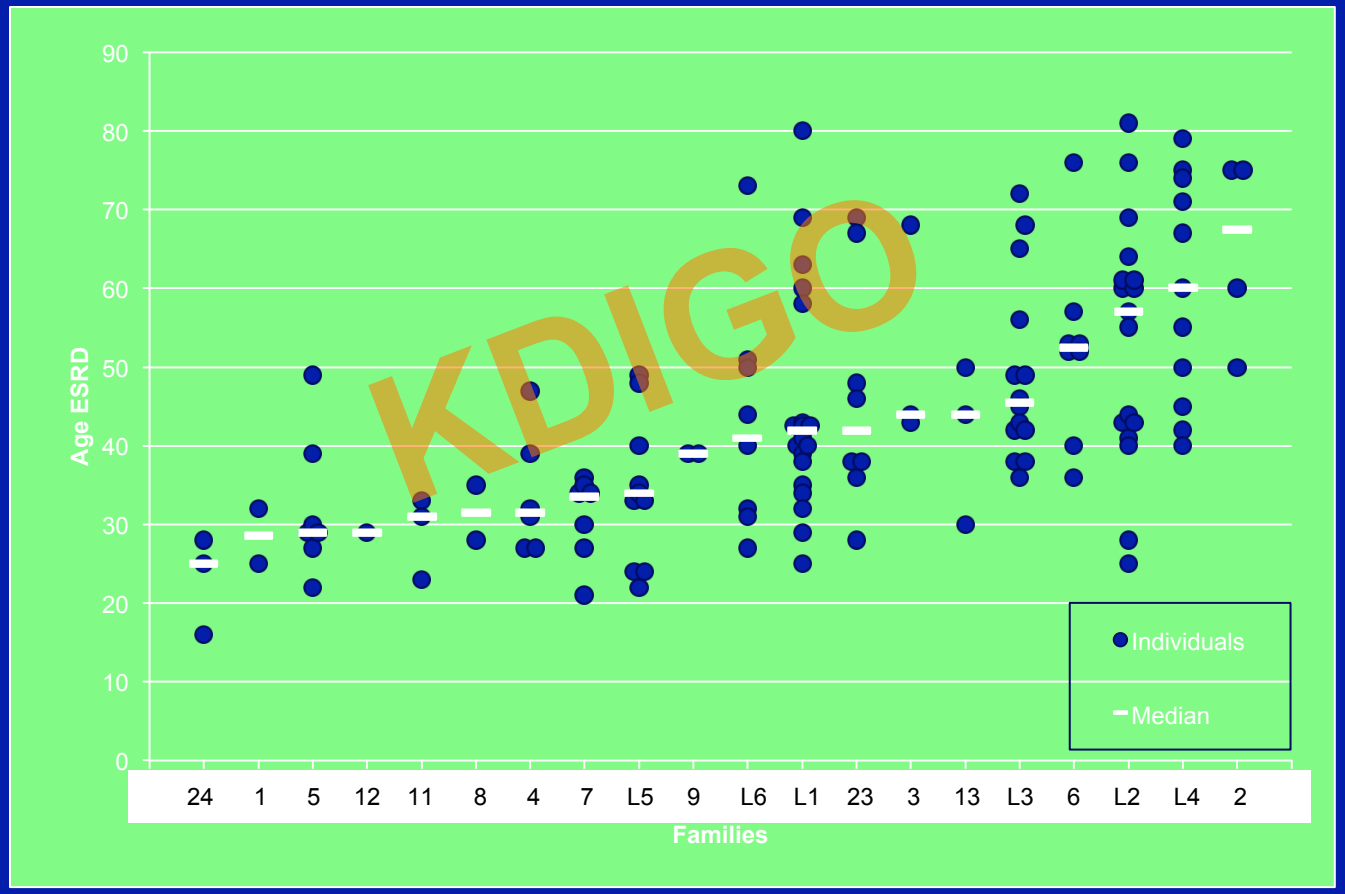
Genotyping Assay

- Specific for c nucleotide insertion
- These samples are being analyzed at the Broad.
- Samples are sent to me, I put them in a plate and send to the Broad.
- Samples should be de-identified.
- There have been problems in getting the testing done. There is a backlog.

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
- Update: now approximately 50 families with MCKD1 mutations

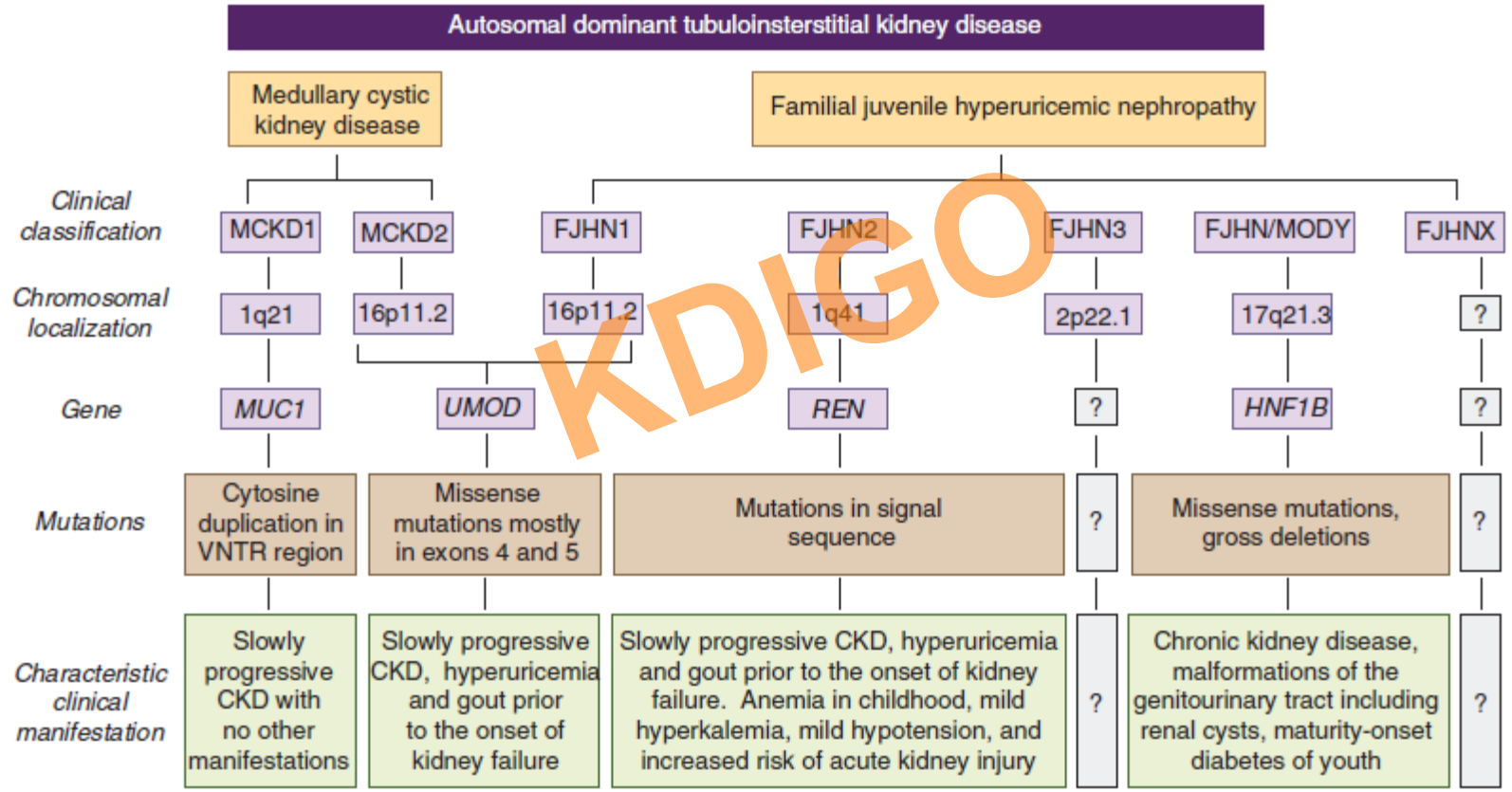
ESRD According to Family



MUC1 I HATE YOU

- The VNTR is large and EXTREMELY difficult to work with.
- 10 years to find the gene
- Huge difficulties with antibodies
- Difficulties with transfection
- Difficulties with mouse development
- The disease is entirely nonspecific and variable in presentation.

- We have been referred 500 families
- Obtained samples in 164 families.
- UMOD 51
- MU1 32
- REN 5
- I believe about 10 to 20% of ADTKD is unexplained.


Autosomal dominant tubulointerstitial kidney disease
Medullary cystic kidney disease
Familial juvenile hyperuricemic nephropathy
Clinical classification
Chromosomal localization
Gene
Mutations
Characteristic clinical manifestation
MCKD1
MCKD2
FJHN1
FJHN2
FJHN3
FJHN/MODY
FJHNX
1q21
16p11.2
16p11.2
1q41
2p22.1
17q21.3
?
MUC1
UMOD
REN
?
HNF1B
?
Cytosine duplication in VNTR region
Missense mutations mostly in exons 4 and 5
Mutations in signal sequence
?
Missense mutations, gross deletions
?
Slowly progressive CKD with no other manifestations
Slowly progressive CKD, hyperuricemia and gout prior to the onset of kidney failure
Slowly progressive CKD, hyperuricemia and gout prior to the onset of kidney failure. Anemia in childhood, mild hyperkalemia, mild hypotension, and increased risk of acute kidney injury
?
Chronic kidney disease, malformations of the genitourinary tract including renal cysts, maturity-onset diabetes of youth
?
KDIGO

Stan Kmoch